Dexmedetomidine as anesthetic adjuvant : cardiovascular and anesthetic effects in animals and humans

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PROEFSCHRIFT

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For Gordana, in gratitude, love and respect

By doubting we are led to enquire;
By enquiry we perceive the truth.
Pierre Abelard, 12th century

Something unknown is doing we don't know what.
Sir Arthur Eddington

There is in us something wiser than our head.
Arthur Schopenhauer

Contents

CHAPTER 1

Introduction

In the early days of anesthesia a single agent such as ether was used to provide surgical anesthesia. High doses of this single agent were often required, resulting in delayed recovery and persistent nausea and vomiting. In modern, so-called 'balanced' anesthesia the total dose of anesthetic agent is reduced by using separate agents to provide the triad of sleep, pain relief, and muscle relaxation. By balancing the agents used, side-effects can be reduced and the quality of post-operative recovery improved. In addition, sedative drugs may be used as premedicants or adjuvants to further reduce the dose of the primary anesthetics. Benzodiazepines are frequently used in this context.

To further improve the quality of anesthesia, anesthesiologists have become interested in α_2-adrenergic receptor agonists since these agents have been shown to have an interesting combination of effects: sedation [1,2], anxiolysis [3,4], reduction of anesthetic requirements [5,6], and improved hemodynamic stability in the peri-operative period [7–9]. In addition, they provide analgesia which is not mediated via opiate receptors [10] and which is not associated with respiratory depression [11]. In veterinary anesthesia, α_2-adrenergic receptor agonists were introduced as sedatives and anesthetic adjuvants in the 1980's and are now commonly used in this field [12–15].

Clonidine, an α_2-adrenergic agonist, which was first introduced into clinical use 25 years ago as an anti-hypertensive agent, has been extensively studied as a potential anesthetic adjuvant in a variety of settings including aortic and coronary artery surgery [7–9,16–18]. Dexmedetomidine is one of the second generation of α_2-adrenergic agonists, and is a full agonist with a high selectivity for the α_2-adrenergic receptor (1600:1 α_2:α_1, compared to 200:1 for clonidine) [19,20]. It has been shown to possess a greater anesthetic-sparing effect than clonidine in animals [21], and to have sedative [22] and hemodynamic stabilizing effects in human volunteers [23].

While these properties suggested promising anesthetic possibilities for selective α_2-agonists like dexmedetomidine, studies in animals showed cardiovascular effects which might be undesirable in a potential anesthetic adjuvant: Flacke *et al.* demonstrated the high vasoconstrictive potency of dexmedetomidine [24], and Heusch

and his coworkers indicated that α_2-adrenergic receptor stimulation could under certain conditions elicit myocardial ischemia [25–27].

1.1 Aims of the studies

In order to test the hypothesis that dexmedetomidine can be beneficially and safely used during anesthesia in healthy adults we developed two main aims:

1. Evaluation of the cardiovascular effects of dexmedetomidine in animals
2. Evaluation of dexmedetomidine as an anesthetic adjuvant in man

To the first purpose we designed the following studies:

- Comparison of the systemic and coronary hemodynamic effects of dexmedetomidine with those of clonidine in dogs (Chapter 4)
- The effects of dexmedetomidine on the balance of myocardial oxygen supply and demand (Chapter 5)
- The effect of dexmedetomidine on nutrient blood supply to the major organ systems (Chapter 6). As anesthesia may interact with the effects of dexmedetomidine, two different anesthetic techniques were used in these canine studies.
- The hemodynamic and coronary effects of dexmedetomidine in goats (Chapter 7). This study was designed to ascertain whether species is important.

To the second purpose a double-blind placebo-controlled study was designed to investigate the potential benefits of dexmedetomidine when given as a single intravenous dose prior to minor surgery in healthy patients (Chapter 8).

References

1 Scheinin M, Kallio A, Koulu M, Viikari J, Scheinin H. Sedative and cardiovascular effects of medetomidine, a novel selective alpha 2-adrenoceptor agonist, in healthy volunteers. *Br J Clin Pharmacol* 1987; **24**: 443–51.

2 Vaha VT. Clinical evaluation of medetomidine, a novel sedative and analgesic drug for dogs and cats. *Acta Vet Scand* 1989; **30**: 267–73.

3 Redmond D. Does clonidine alter anxiety in humans? *Trends Pharmacol Sci* 1982; **3**: 477–80.

4 Hoehn-Saric R, Merchant A, Keyser M, Smith V. Effects of clonidine on anxiety disorders. *Arch Gen Psychiatry* 1981; **38**: 1278–82.

5 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5.

6 Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg* 1982; **61**: 741–5.

7 Ghignone M, Quintin L, Duke P, Kehler C, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.

8 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.

9 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

10 Spaulding TC, Fielding S, Venafro JJ, Lal H. Antinocioceptive activity of clonidine and its potentiation of morphine analgesia. *Eur J Pharmacol* 1979; **58**: 19–25.

11 Bailey PL, Sperry RJ, Johnson GK, *et al.* Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology* 1991; **74**: 43–8.

12 Jalanka H. The use of medetomidine, medetomidine-ketamine combinations and atipamezole at Helsinki Zoo—a review of 240 cases. *Acta Vet Scand Suppl* 1989; **85**: 193–7.

13 Mero M, Vainionpaa S, Vasenius J, Vihtonen K, Rokkanen P. Medetomidine-ketamine-diazepam anesthesia in the rabbit. *Acta Vet Scand Suppl* 1989; **85**: 135–7.

14 Verstegen J, Fargetton X, Ectors F. Medetomidine/ketamine anaesthesia in cats. *Acta Vet Scand Suppl* 1989; **85**: 117–23.

15 Vaha VT. The clinical efficacy of medetomidine. *Acta Vet Scand Suppl* 1989; **85**: 151–3.

16 Engelman E, Lipszyc M, Gilbart E, *et al.* Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–87.

17 Quintin L, Roudot F, Roux C, *et al.* Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *Br J Anaesth* 1991; **66**: 108–15.

18 Quintin L, Viale JP, Annat G, *et al.* Oxygen uptake after major abdominal surgery: effect of clonidine. *Anesthesiology* 1991; **74**: 236–41.

19 Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Karki NT. Evidence for medetomidine as a selective and potent agonist at alpha 2-adrenoreceptors. *J Auton Pharmacol* 1986; **6**: 275–84.

20 Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine—a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; **13**: 635–51.

21 Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. *Anesthesiology* 1988; **69**: 818–23.

22 Kallio A, Salonen M, Forssell H, Scheinin H, Scheinin M, Tuominen J. Medetomidine premedication in dental surgery—a double-blind cross-over study with a new alpha 2-adrenoceptor agonist. *Acta Anaesthesiol Scand* 1990; **34**: 171–5.

23 Kallio A, Scheinin M, Koulu M, *et al.* Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. *Clin Pharmacol Ther* 1989; **46**: 33–42.

24 Flacke JW, Flacke WE, Bloor BC, McIntee DF. Hemodynamic effects of dexmedetomidine, an alpha 2-adrenergic agonist, in autonomically denervated dogs. *J Cardiovasc Pharmacol* 1990; **16**: 616–23.

25 Seitelberger R, Guth B, Heusch G, Lee J, Katayama K, Ross JJ. Intracoronary alpha 2-adrenergic receptor blockade attenuates ischemia in conscious dogs during exercise. *Circ Res* 1988; **62**: 436–42.

26 Heusch G, Deussen A. The effects of cardiac sympathetic nerve stimulation on the perfusion of stenotic coronary arteries in the dog. *Circ Res* 1983; **53**: 8–15.

27 Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation* 1990; **81**: 1–13.

CHAPTER 2

Pharmacology of the α_2-adrenergic receptor - a review of the literature

2.1 History

In 1948, Alquist [1] first subdivided the adrenergic receptors into α and β based on their pharmacological properties. He used five different catecholamines and found that their rank order of potency was different for two distinct physiological functions. Almost 20 years later Lands *et al.* [2] subdivided both the α and β-adrenergic receptors into α_1 and α_2, and β_1 and β_2 subtypes. The α-adrenoceptors were divided into α_1 and α_2 largely based on function, α_1 being excitatory and α_2 inhibitory [3] or location, α_1 being presynaptic and α_2 postsynaptic [4]. Neither of these classifications proved to be completely correct, and α_2-adrenoceptors are now known to be located both pre- and post-synaptically and elicit a complex profile of pharmacological actions.

Four α_2-adrenoceptor subtypes have now been described: the α_{2A}, α_{2B}, α_{2C} and α_{2D}. They have been differentiated by the relative affinities to radio-labelled antagonists [5].

2.2 Molecular pharmacology

The α_2-adrenoceptor is a member of the G protein-coupled family of cell membrane receptors which transduce their biological responses by activating pertussis toxin-sensitive [6], guanine-nucleotide binding regulatory proteins (G-proteins) [7,8]. The α_2-receptor proteins are monomeric polypeptides between 450 and 461 amino acids in length (complete amino acid sequencies are known for both human and rat receptors) [9,10]. The most characteristic structural feature in the suggested secondary structure of these receptor proteins is the presence of seven stretches of 20–25 hydrophobic amino acids which are thought to span the plasma membrane in an α-helical fashion. These transmembrane domains are separated by extra- and intra-cellular loops formed of hydrophilic amino acids [7,11].

The G proteins are responsible for transducing the signal to an intracellular effector system. 3',5'-Cyclic adenosine monophosphate (cAMP) is an important regulator of many cellular functions. Specific cAMP-dependent kinases modify the activity of target proteins by controlling their phosphorylation status. Inhibition of adenylyl cyclase, which results in decreased formation of cAMP, is an important consequence of α_2-adrenoceptor activation. This effect can be seen in virtually every system examined so far. Increased intracellular availability of Ca^{2+} is indisputably involved in the smooth muscle contracting effect of α_2-adrenergic agonists, and vasoconstriction mediated by α_2-adrenoceptors can be attenuated or abolished by Ca^{2+}-chelating agents [12].

2.3 The α_2-adrenergic agonists

Clonidine and dexmedetomidine are both α_2-adrenergic agonists (see Figure 2-1).

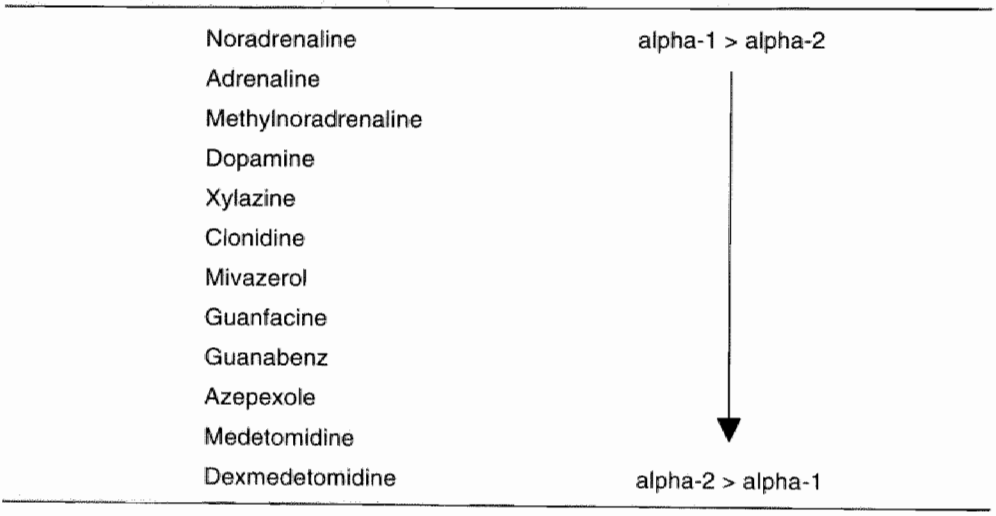


Figure 2-1 α_2-Adrenergic agonists from most alpha-1 to most alpha-2 (after P. Talke, personal communication).

2.3.1 Clonidine

Clonidine (see Figure 2-2) is the prototypical α_2-adrenoceptor agonist to which all other α_2-agonists are compared. Its actions are mediated mainly by α_2-adrenoceptors, but it is a weak α_1-agonist as well (200:1 α_2:α_1). The predominant effects of clonidine in human subjects include reductions in blood pressure and heart rate, sedation, decreased salivation, and a decline in plasma catecholamine concentrations indicating reduced sympathetic activity [13]. Clonidine has been used clinically for 25 years in the treatment of hypertension [14], congestive heart failure [15] and to reduce

myocardial ischemia and infarct size [16–18]. It has also been successfully used in connection with opioid [19] and alcohol withdrawal syndromes [20].

2.3.2 *Dexmedetomidine*

Dexmedetomidine (see Figure 2-2) is the pharmacologically active δ-isomer of medetomidine, a novel lipophilic imidazole derivative with a high affinity for α_2-adrenoceptors (1600:1 α_2:α_1) [21–24]. The pharmacological actions of dexmedetomidine closely resemble those of clonidine, but dexmedetomidine has been reported to be a complete anesthetic by itself in sufficiently high doses in experimental animals [25].

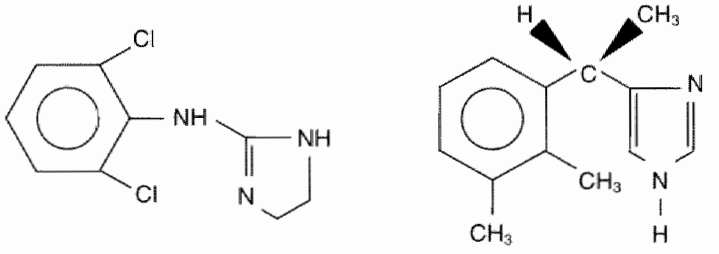
Table 2-1 Examples of α-adrenergic antagonists

Non-selective α-adrenoceptor antagonists	α_1-Adrenoceptor antagonists	α_2-Adrenoceptor antagonists
Phentolamine	Prazosin	Yohimbine
Tolazoline	Terazosin	Rauwolscine
	Doxazosin	Idazoxan
	Trimazosin	Atipamezole
	Corynanthine	
	Phenoxybenzamine	
	Labetolol	

Modified after Bloor [26].

2.4 The α-adrenergic antagonists

Antagonists are used frequently in pharmacological studies to differentiate between different pharmacological effects of a drug. The α_2-adrenoceptor antagonist atipamezole, has been shown to antagonise the hemodynamic, catecholamine and sedatory



Clonidine Dexmedetomidine

Figure 2-2 Structure of clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline) and dexmedetomidine (4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole).

effects of dexmedetomidine in humans [27, 28]. Atipamezole is now used routinely in veterinary practice to reverse the sedative and cardiovascular effects of medetomidine and dexmedetomidine [29–32]. Atipamezole and other α-adrenergic antagonists are listed in Table 2-1.

2.5 Central nervous system sites involved in the α_2-adrenoceptor-mediated antihypertension and bradycardia

Central antihypertensive and bradycardic actions of the α_2-adrenergic agonists are mediated at a variety of binding sites in several brainstem visceral nuclei – especially the nucleus tractus solitarius (NTS), the rostral ventrolateral medulla (C1 area), the caudal ventrolateral medulla (A1 area including the lateral reticular nucleus), the dorsal motor nucleus of the vagus (DMV), the nucleus commissuralis (NC), and the locus coeruleus (LC) [33,34]. Reciprocal connections exist between nearly all of these areas.

The actions of α_2-adrenergic agonists on these areas are complex. Microinjection of α_2-adrenergic agonists into the NTS or DMV induce bradycardia with less hypotension while microinjection into the rostral ventral lateral medulla (C1 area) is associated with the induction of hypotension [33,35–37].

The bradycardic effect of α_2-adrenergic agonists is complex, but is thought to be due to a combination of presynaptic inhibition of noradrenaline release at cardiac sympathetic nerve terminals and central reduction of sympathetic drive plus facilitation of the baroreceptor reflex [38,39].

The LC is a region in the dorso-lateral pons with a high concentration of α_2-adrenergic binding sites [34]. It has been shown that α_2-adrenergic agonists alter cellular firing in the LC, and that electrical or chemical stimulation of the LC alters systemic arterial pressure [40,41]. The LC has also been shown to be a major site of action for the sedative/hypnotic effect of α_2-adrenergic agonists, and implicated in the anesthetic reducing and hemodynamic stabilising actions of clonidine and dexmedetomidine [42–44] (see also Chapter 3.2). It is not known whether there is an interaction between the sedative/hypnotic and cardiovascular effects of α_2-adrenergic agonists on the LC.

It is probable that the effect of an α_2-adrenergic agonist on sympathetic and parasympathetic tone is dependent on pre-existing endogenous tone. A high sympathetic tone may predispose to a more profound hemodynamic effect following administration of an α_2-adrenergic agonist [45].

2.6 Imidazoline receptors

It has been suggested that the central hypotensive effect of clonidine-like substances could be due to their interaction with receptors distinct from the α_2-adrenergic receptors specifically recognizing their imidazoline structure [46] within the rostral ventrolateral medulla [35,36]. Such 'imidazoline-preferring' receptors have since been identified in the brain [47] and other organs, and have been differentiated into I_1 and I_2 subtypes.

Several α_2-adrenergic agonists (clonidine, rilmenidine, tizanidine and moxonidine) show high affinity for I_1 receptors [48–52]. A centrally-mediated sympatholytic effect can be induced by both α_2-adrenergic and I_1 receptor agonists [53].

It has proved difficult to dissociate imidazoline from α_2-receptors both pharmacologically and functionally; all I_1 receptor agonists have comparable affinity for α_2-receptors and there is no selective antagonist for I_1 compared to α_2-receptors. While there are subtle differences in distribution, most central nervous system nuclei contain both receptors. There appears to be a difference in the receptor involved depending on the mode of administration of the agonist. For example, clonidine induces hypotension via I_1 receptors if given directly into the rostral ventrolateral medulla (RVLM), but via α_2-adrenergic receptors if given intravenously [54].

The elucidation of the imidazoline receptor is of importance since it may be possible to develop drugs with more or less affinity for the two receptors, thereby producing selectively sedation without hemodynamic effects and vice versa. The actions of rilmenidine as an antihypertensive with minimal sedation is an initial attempt at such discrimination [55].

2.7 Peripheral vasoconstriction

Both α_1- and α_2-adrenoceptors are known to be present on vascular smooth muscle [56]. The pressor effect of exogenously administered cathecholamines in the pithed rat can be blocked by α_2-adrenoceptor antagonists, while the pressor response evoked by sympathetic nerve stimulation is antagonised by α_1-adrenoceptor antagonists [57]. Therefore, it is likely that the sympathetic junctional receptor in systemic arterial vasculature is an α_1-adrenoceptor while the extrajunctional adrenoceptor (which responds to circulating catecholamine) is of the α_2 type [58].

Postjunctional α_2-adrenoceptors mediate both arterial and venous vasoconstriction [56]. Alpha-adrenoceptors mediating vasoconstriction appear to differ in their utilisation of calcium ions. Although there are species differences, in general, vascular α_1-adrenoceptor agonists promote vasoconstriction by utilising intracellular calcium while α_2-adrenoceptor mediated vasoconstriction uses extracellular calcium. This may

be why calcium channel blockers are effective in blocking α_2-adrenoceptor induced vasoconstriction [59].

2.8 Hemodynamic effects of α_2-adrenergic receptor agonists

The characteristic response to intravenous administration of an α_2-adrenergic receptor agonist in a normotensive or hypertensive animal and man is an immediate pressor response, caused by stimulation of peripheral arterial postjunctional α_2-adrenergic receptors [60–62]. This pressor response is relatively short-lived and is followed by a slow decline in arterial blood pressure to levels lower than those observed prior to drug administration. This long-lasting depressor/antihypertensive response is a result of central α_2-adrenergic receptor stimulation. Heart rate declines immediately following administration and continues to be reduced for the duration of drug action. If the α_2-adrenergic receptor agonist is administered directly into the central nervous system or via the vertebral artery, which allows for easy access to the central nervous system, the initial pressor resonse is not observed [60,63]. The oral administration of α_2-adrenergic agonists, such as clonidine and dexmedetomidine, does not cause a pressor response prior to the centrally mediated reduction in systemic blood pressure [64]. Studies have also shown that the volatile anesthetics, halothane and isoflurane, may attenuate the vasoconstrictor responses of α_2-adrenergic agonists [65,66]

The bradycardia associated with α_2-adrenergic receptor agonists may result, in part, from a peripheral presynaptic action at prejunctional α_2-adrenergic receptors on sympathetic nerves to the heart, since heart rate can be reduced in pithed rats [67,68]. Also, in the anesthetized rat, α_2-adrenergic receptor agonist-induced bradycardia does not require penetration into the central nervous system while hypotension does [69].

2.8.1 Cardiac function

α_2-Adrenoceptor agonists reduce cardiac output in dogs [59], humans [62], and in most other species studied till now. The mechanism for this decrease in pump function is still a matter for discussion [59,70].

α_2-Adrenergic agonists have no direct effects on myocardial cells. Housmans found that dexmedetomidine had no effects on ferret papillary muscle [71] while Flacke *et al.* demonstrated that dexmedetomidine had no direct effects on the isolated dog heart [72].

α_2-Adrenoceptor stimulation can affect the contractility of the heart via the centrally mediated reduction in sympathetic tone, leading to reduced activity of cardiac sympathetic nerves and lower circulating catecholamines. In addition, stimulation of α_2-adrenergic receptors on the cardiac sympathetic nerve terminals can also cause a reduction in contractility by diminishing noradrenaline release from these nerves.

The negative inotropic effects of the selective α_2-adrenergic agonists have also been attributed to harmful coronary vasoconstriction. The limitation of oxygen supply to the heart thus induced could reduce pump function [73]. The fact that cardiac output is reduced in denervated animals where no central sympatholytic effect is present has been presented as evidence for this view [70]. This question will be addressed in more detail in this thesis.

2.9 Organ blood flow

2.9.1 Myocardial blood flow

Adrenaline or noradrenaline administered directly into the coronary artery, or cardiac sympathetic nerve stimulation in the dog [74–78], rat [79], cat [78], monkey [78], and guinea-pig [80] results in a transient decrease, followed by a longer-lasting increase in coronary blood flow. The initial transient decrease is believed to be mediated by α-adrenoceptors [77], whereas the vasodilation is believed to be mediated by β-adrenoceptors [81]. It has been suggested that α_2-adrenergic receptor-mediated coronary vasoconstriction can cause myocardial ischemia [82]. The coronary circulation appears to be able to adjust to chronic adrenergic stimulation as is shown by the fact that vasoconstriction does not occur after sustained stimulation [83].

Although it is obvious that exaggerated α-adrenergic vasoconstriction is deleterious, there is continuing debate on its relevance under (patho)physiological conditions. Coronary blood flow is strongly controlled by a metabolically driven autoregulation [84]. Coronary artery blood flow is also impeded by systolic contraction. This effect is more pronounced in the inner than the outer layers of the left ventricle [85]. Thus coronary blood flow to the endocardium occurs only during diastole which results in a reduction in the time available for flow to the endocardium during tachycardia. Feigl *et al.* have provided evidence that selective epicardial adrenergic vasoconstriction helps maintain a uniform transmural blood flow in the left ventricle during tachycardia and sympathetically mediated stress [81]. Whereas vasodilation "steals" blood from the endocardium, selective epicardial vasoconstriction would serve to maintain uniform perfusion (a so-called "anti-steal" effect).

2.9.2 Cerebral blood flow

Both clonidine and dexmedetomidine have been shown to reduce cerebral blood flow (CBF) in animals [86,87] possibly due to direct stimulation of α_2-adrenoceptors in the cerebral vasculature [88]. A reduction in cerebral blood flow after clonidine has also been shown in humans [89]. However, in patients with acute hypertension significant individual variation was seen, an increase where initial CBF was low, and a decrease where the initial CBF was high [90]. In studies in which a decrease in CBF has been demonstrated, the dogs were anesthetized with either halothane [86] or isoflurane [87]

which are known to cause cerebral vasodilation. Moreover, in neither of these studies was there a significant decrease in the cerebral metabolic rate for oxygen ($CMRO_2$), suggesting no significant cerebral ischemia developed. On the contrary, other studies have suggested that α_2-adrenoceptor agonists may improve neurological outcome following cerebral ischaemia [91,92].

2.9.3 *Renal blood flow*

Administration of α_2-adrenergic antagonists in the renal artery of hypertensive patients increased renal blood flow, yohimbine being more potent than doxazosin [93]. However, in hypertensive rats, acute reduction of blood pressure by 20% by clonidine did not reduce renal blood flow probably because of the renal sympathetic nerve blocking action of clonidine [94]. Moreover, α_2-adrenergic activation has been shown to alter renal function increasing sodium and water excretion. In a human study during anesthesia for otorhinolaryngeal or orthopedic surgery, clonidine 5 μg/kg increased urine production [95]. It has also been postulated that renin release is inhibited by activation of the α_2-adrenoceptors in the juxtaglomerular apparatus in the rat [96].

2.9.4 *Cutaneous flow*

Finger blood flow, measured by plethysmography, decreases after administration of clonidine in human subjects [97]. This technique measures gross blood flow, including flow through arterio-venous anastomoses. It has been shown that in extremities shunt flow accounts for a considerable part of total blood flow and the role of α_2-adrenoceptors in regulation of shunt flow is well known [97,98]. The decrease in cutaneous blood flow, and (part of) the decrease in shunt flow, might be related to the role of α_2-adrenoceptors in thermoregulation [99]. Observations that clonidine reduced post-operative shivering seems to agree with this idea [100,101].

References

1 Alquist RP. A study of the adrenotropic receptors. *Am J Physiol* 1948; **153**: 586–600.
2 Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TGJ. Differentiation of receptor systems activated by sympathomimeticamines. *Nature* 1967; **214**: 597–8.
3 Berthelsen S, Pettinger WA. A functional basis for classification of alpha-adrenergic receptors. *Life Sci* 1977; **21**: 595–606.
4 Anden NE, Corrodi H, Fuxe K, Hokfelt B, Hokfelt T, Rydin C. Evidence for a central noradrenaline receptor stimulation by clonidine. *Life Sci* 1970; **9**: 513–23.
5 Bylund DB. Subtypes of alpha 1- and alpha 2-adrenergic receptors. *FASEB J* 1992; **6**: 832–9.
6 Correa-Sales C, Reid K, Maze M. Pertussis toxin-mediated ribosylation of G proteins blocks the hypnotic response to an alpha 2-agonist in the locus coeruleus of the rat. *Pharmacol Biochem Behav* 1992; **43**: 723–7.
7 Dohlman HG, Thorner J, Caron MG, Lefkowitz RJ. Model systems for the study of seven-transmembrane-segment receptors. *Annual Review of Biochemistry* 1991; **60**: 653–88.

8 Birnbaumer L, Abramowitz J, Brown AM. Receptor-effectors coupling by G proteins. *Biochem Biophys Acta* 1990; **1031**: 163–224.

9 Harrison JK, Pearson WR, Lynch K. Molecular characterization of α_1- and α_2-adrenoceptors. *Trends in Pharmacological Science* 1991; **12**: 62–7.

10 Lomasney JK, Cotecchia S, Lefkowitz RJ, Caron MG. Molecular biology of α-adrenergic receptors: implications for receptor classification and for structure-function relationships. *Biochem Biophys Acta* 1991; **1095**: 127–39.

11 Kobilka BK, Matsui H, Kobilka TS, *et al*. Cloning, sequencing, and expression of the gene coding for the human platelet α_2-adrenergic receptor. *Science* 1987; **238**: 650–6.

12 Ruffolo RR, Nichols AJ, Stadel JM, Hieble JP. Structure and function of α-adrenoceptors. *Pharmacol Rev* 1991; **43**: 475–505.

13 van Zwieten PA. Drugs interacting with alpha adrenoceptors. *Cardiovasc Drugs Ther* 1989; **3**: 121–33.

14 Mitrovic V, Hallier E, Kuschke HJ. The haemodynamic effects of clonidine in patients with grade III to IV hypertension. *J Cardiovasc Pharmacol* 1986; **8**: S51–5.

15 Magorien RD, Hermiller JB, Unverferth DV, Leier CV. Regional hemodynamic effects of clonidine in congestive heart failure. *J Cardiovasc Pharmacol* 1985; **7**: 91–6.

16 Foresti A, Massari FM, Lotto A. Hemodynamic effects of clonidine in patients with acute myocardial infarction complicated by hypertension. *J Cardiovasc Pharmacol* 1986; **8**: S30–2.

17 Zochowski R. Intravenous clonidine in acute myocardial infarction in men. *Int J Cardiol* 1984; **6**: 189–205.

18 Renard M, Liebens I, Waterschoot P, Bernard R. Central inhibition of sympathetic overdrive by clonidine in acute myocardial infarction with systolic hypertension. Haemodynamic study. *Angiology* 1986; **37**: 633–41.

19 Gold MS, Pottash AC, Sweeney DR, Klever HD. Opiate withdrawal using clonidine. A safe, effective, and rapid nonopiate treatment. *JAMA* 1980; **243**: 343–6.

20 Wilkins AJ, Jenkins WJ, Steiner JA. Efficacy of clonidine in treatment of alcohol withdrawal state. *Psychopharmacology* 1983; **81**: 78–80.

21 Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Karki NT. Evidence for medetomidine as a selective and potent agonist at alpha 2-adrenoreceptors. *J Auton Pharmacol* 1986; **6**: 275–84.

22 Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine–a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; **13**: 635–51.

23 MacDonald E, Scheinin M, Scheinin H, Virtanen R. Comparison of the behavioral and neurochemical effects of the two optical enantiomers of medetomidine, a selective alpha-2-adrenoceptor agonist. *J Pharmacol Exp Ther* 1991; **259**: 848–54.

24 MacDonald E, Scheinin H, Scheinin M. Behavioural and neurochemical effects of medetomidine, a novel veterinary sedative. *Eur J Pharmacol* 1988; **158**: 119–27.

25 Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha 2-adrenergic agonist, in halothane-anesthetized dogs. *Anesth Analg* 1988; **67**: 611–5.

26 Bloor B. General pharmacology of α_2-adrenoceptors. *Anaesth Pharmacol Rev* 1993; **1**: 221–32.

27 Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha 2-adrenoceptor agonist effects by atipamezole in human volunteers. *Br J Clin Pharmacol* 1991; **31**: 160–5.

28 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. *J Clin Anesth* 1993; **5**: 194–203.

29 Jones RS, Young LE. Medetomidine premedication in dogs and its reversal by atipamezole. *Acta Vet Scand Suppl* 1991; **87**: 165–7.

30 Vaha VA. The clinical effectiveness of atipamezole as a medetomidine antagonist in the dog. *J Vet Pharmacol Ther* 1990; **13**: 198–205.
31 Vainio O, Vaha VT. Reversal of medetomidine sedation by atipamezole in dogs. *J Vet Pharmacol Ther* 1990; **13**: 15–22.
32 Vainio O. Reversal of medetomidine-induced cardiovascular and respiratory changes with atipamezole in dogs. *Vet Rec* 1990; **127**: 447–50.
33 Unnerstall JR, Kopajtic TA, Kuhar MJ. Distribution of alpha 2 agonist binding sites in the rat and human central nervous system: analysis of some of functional, anatomical correlates of the pharmacological effects of clonidine and related adrenergic agents. *Brain Res* 1984; **319**: 69–101.
34 Unnerstall J, Kuhar M. Mapping the α_2-adrenergic receptor in the central nervous system: a guide to structure and function., Epinephrine in the central nervous system. Edited by Stolk J, U'Prichard D, Fuxe K. New York, Oxford University Press, 1988, pp 45–59.
35 Bousquet P, Feldman J, Velly J, Bloch R. Role of the ventral surface of the brain stem in the hypotensive action of clonidine. *Eur J Pharmacol* 1975; **34**: 151–6.
36 Bousquet P, Feldman J, Bloch R, Schwartz J. The nucleus reticularis lateralis: a region highly sensitive to clonidine. *Eur J Pharmacol* 1981; **69**: 389–92.
37 Reis DJ, Morrison S, Ruggiero DA. The C1 area of the brainstem in tonic and reflex control of the circulation. *Hypertension* 1988; **11**: I8–13.
38 Cavero I, Roach AG. Effects of clonidine on canine cardiac neuroeffector structures controlling heart rate. *Br J Pharmacol* 1980; **70**: 269–76.
39 de Jonge A, Timmermans P, van Zwieten P. Quantitative aspects of alpha adrenergic effects induced by clonidine-like imidazolidines. II. Central and peripheral bradycardic activities. *J Pharmacol Exp Ther* 1982; **222**: 712–9.
40 Sved A, Felsten G. Stimulation of the locus coeruleus decreases arterial pressure. *Brain Res* 1987; **414**: 119–32.
41 Gurtu S, Pant K, Sinha J, Bhargava K. An investigation into the mechanism of cardiovascular responses elicited by electrical stimulation of locus coeruleus and subcoeruleus in the cat. *Brain Res* 1984; **301**: 59–64.
42 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605.
43 Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology* 1989; **71**: 75–9.
44 Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats [see comments]. *Anesthesiology* 1992; **76**: 948–52.
45 Muzi M, Golf D, Kampine J, Roerig D, Ebert T. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. *Anesthesiology* 1992; **77**: 864–71.
46 Bousquet P, Feldman J, Schwartz J. Central cardiovascular effects of alpha adrenergic drugs. Difference between catecholamines and imidazolines. *J Pharmacol Exp Ther* 1984; **230**: 232–6.
47 Ernsberger P, Meeley M, Mann J, Reis D. Clonidine binds to imidazole binding sites as well as alpha 2-adrenoceptors in the ventrolateral medulla. *Eur J Pharmacol* 1987; **134**: 1–13.
48 Ernsberger P, Damon T, Graff L, Schafer S, Christian M. Moxonidine, a centrally acting antihypertensive agent, is a selective ligend for I_1-imidazoline sites. *J Pharmacol Exp Ther* 1993; **264**: 172–82.
49 Taittonen M, Raty H, Kirvela O, Aantaa R, Kanto J. The metabolic effects of oral tizanidine in healthy volunteers. *Acta Anaesthesiol Scand* 1995; **39**: 628–32.
50 Tibirica E, Feldman J, Mermet C, Gonon F, Bousquet P. An imidazoline-specific mechanism for the hypotensive effect of clonidine: a study with yohimbine and idazoxan. *J Pharmacol Exp Ther* 1991; **256**: 606–13.

51 Tibirica E, Feldman J, Mermet C, Monassier L, Gonon F, Bousquet P. Selectivity of rilmenidine for the nucleus reticularis lateralis, a ventrolateral medullary structure containing imidazoline-preferring receptors. *Eur J Pharmacol* 1991; **209**: 213–21.

52 Ernsberger P, Giuliano R, Willette R, Reis D. Role of imidazole receptors in the vasodepressor response to clonidine analogs in the rostral ventrolateral medulla. *J Pharmacol Exp Ther* 1990; **253**: 408–18.

53 Gomez R, Ernsberger P, Feinland G, Reis D. Rilmenidine lowers arterial pressure via imidazol receptors in brainstem C1 area. *Eur J Pharmacol* 1991; **195**: 181–91.

54 Hieble JP, Ruffolo RJ. Possible structural and functional relationships between imidazoline receptors and alpha 2-adrenoceptors. *Ann N Y Acad Sci* 1995; **763**: 8–21.

55 Bousquet P, Feldman J, Tibirica E, *et al*. New concepts on the central regulation of blood pressure. Alpha2-adrenoceptors and "imidazoline receptors". *Am J Med* 1989; **87**: 10S–13S.

56 Drew G, Whiting S. Evidence for two distinct types of postsynaptic alpha-adrenoceptor in vascular smooth muscle in vivo. *Br J Pharmacol* 1979; **67**: 207–15.

57 Yamaguchi I, Kopin IJ. Differential inhibition of alpha-1 and alpha-2 adrenoceptor-mediated pressor response in pithed rats. *J Pharmacol Exp Ther* 1980; **214**: 275–81.

58 Langer SZ, Shepperson NB. Recent developments in vascular smooth muscle pharmacology: the post-synaptic alpha-2-adrenoceptor. *TIPS* 1982; **3**: 440–4.

59 Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M. Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992; **263**: 690–7.

60 Ruffolo RR, Goldberg MR, Morgan EL. Receptor interactions of imidazolines. X1. α-adrenergic and antihypertensive effects of clonidine and its methylene-bridged analog, St 1913. *Pharmacology* 1982; **25**: 187–201.

61 Onesti G, Schwartz AB, Kim KE. Antihypertensive effect of clonidine. *Circ Res* 1971; **28**: 53–69.

62 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42.

63 Timmermans PBMWM, Hoefke W, Stahle H, van Zwieten PA. Structure-activity relationships in clonidine-like imidazolines and related compounds. *Prog Pharmacol* 1980; **3**: 1–104.

64 Proctor LT, Schmeling WT, Roerig D, Kampine JP, Warltier DC. Oral dexmedetomidine attenuates hemodynamic responses during emergence from general anesthesia in chronically instrumented dogs. *Anesthesiology* 1991; **74**: 108–14.

65 Kenny D, Pelc L, Brooks H, Kampine J, Schmeling W, Warltier D. Alterations of alpha-1 and alpha-2 adrenoceptor-mediated pressor responses by halothane and isoflurane anesthesia. *Anesthesiology* 1989; **71**: 224–34.

66 Larach DR, Schuler HG, Derr JA, Larach MG, Hensley FAJ, Zelis R. Halothane selectively attenuates alpha 2-adrenoceptor mediated vasoconstriction, in vivo and in vitro. *Anesthesiology* 1987; **66**: 781–91.

67 Misu Y, Kubo T. Central and peripheral cardiovascular responses of rats to guanbenz and clonidine. *Jpn J Pharmacol* 1982; **32**: 925–8.

68 Drew GM. Effects of alpha-adrenoceptor agonists and antagonists on pre- and postsynaptically located alpha-adrenoceptors. *Eur J Pharmacol* 1976; **36**: 313–20.

69 de Jonge A, Timmermans P, van Zwieten P. Participation of cardiac presynaptic α_2-adrenoceptors in the bradycardic effects of clonidine and analogues. *Naunyn-Schmiedebergs Arch Pharmacol* 1981; **317**: 8–12.

70 Flacke JW, Flacke WE, Bloor BC, McIntee DF. Hemodynamic effects of dexmedetomidine, an alpha 2-adrenergic agonist, in autonomically denervated dogs. *J Cardiovasc Pharmacol* 1990; **16**: 616–23.

71 Housmans PR. Effects of dexmedetomidine on contractility, relaxation, and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990; **73**: 919–22.

72 Flacke WE, Flacke JW, Blow KD, McIntee DF, Bloor BC. Effect of dexmedetomidine, an alpha 2-adrenergic agonist, in the isolated heart. *J Cardiothorac Vasc Anesth* 1992; **6**: 418–23.

73 Flacke WE, Flacke JW, Bloor BC, McIntee DF, Sagan M. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7**: 41–9.

74 Pitt B, Elliot EC, Gregg DE. Adrenergic receptor activity in the coronary arteries of the unanesthetized dog. *Circ Res* 1967; **21**: 75–84.

75 Gall PG, Kattus AA, Kolin A, Ross G. Effects of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade. *Br J Pharmacol* 1966; **26**: 713–22.

76 Lioy F. An analysis of the mechanism of catecholamine effects on coronary circulation. *Am J Physiol* 1967; **213**: 487–91.

77 Malindzak GSJ, Kosinski EJ, Green HD, Yarborough GW. The effects of adrenergic stimulation on conductive and resistive segments of the coronary vascular bed. *J Pharmacol Exp Ther* 1978; **206**: 248–58.

78 Proctor E. The effects of physiological concentrations of noradrenaline on the coronary resistance of isolated perfused hearts of the cat, dog and monkey. *J Pharm Pharmacol* 1968; **20**: 36–40.

79 Glomstein A, Hauge A, Oye I, Sinclair D. Effects of adrenaline on coronary flow in isolated perfused rat hearts. *Acta Physiol Scand* 1967; **69**: 102–10.

80 Broadley KJ. An analysis of the coronary vascular responses to catecholamines, using a modified Langendorff heart preparation. *Br J Pharmacol* 1970; **40**: 617–29.

81 Feigl EO. Adrenergic control of transmural coronary blood flow. *Basic Res Cardiol* 1990; **85**: 167–76.

82 Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation* 1990; **81**: 1–13.

83 Williams DO, Most AS. Responsiveness of the coronary circulation to brief vs sustained alpha-adrenergic stimulation. *Circulation* 1981; **63**: 11–6.

84 Feigl EO. Coronary physiology. *Physiol Rev* 1983; **63**: 1–205.

85 Heineman FW, MacGregor DC, Wilson GJ, Ninomiyer J. Regional and transmural myocardial temperature distribution in cold chemical cardioplegia: significance of critical coronary artery stenosis. *J Thoracic Cardiovascular Surgery* 1981; **81**: 851–9.

86 Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs [see comments]. *Anesth Analg* 1990; **71**: 125–9.

87 Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesth Analg* 1990; **70**: 624–30.

88 Coughlan MG, Lee JG, Bosnjak ZJ, Schmeling WT, Kampine JP, Warltier DC. Direct coronary and cerebral vascular responses to dexmedetomidine. Significance of endogenous nitric oxide synthesis. *Anesthesiology* 1992; **77**: 998–1006.

89 Kaniwata IS, Yaksh TL, Anderson RE, Marsh RW. Effects of clonidine on cerebral blood flow and the response to arterial CO_2. *J Cerebral Blood Flow and Metabolism* 1986; **6**: 358–65.

90 Green CS, Gretler DD, Cervenka K, McCoy CE, Brown FD, Murphy MB. Cerebral blood flow during the acute therapy of severe hypertension with oral clonidine. *Am J Emergency Medicine* 1990; **8**: 293–6.

91 Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Reversal by the alpha 2-adrenergic antagonist atipamezole. *Anesthesiology* 1991; **75**: 328–32.

92 Maier C, Steinberg GK, Sun GH, Zhi GT, Maze M. Neuroprotection by the alpha 2-adrenoreceptor agonist dexmedetomidine in a focal model of cerebral ischemia. *Anesthesiology* 1993; **79**: 306–12.

93 de Leeuw PW, van Es PN, de Bos R, Birkenhager WH. Role of alpha 1- and alpha 2-adrenergic receptors in the human hypertensive kidney. *Hypertension* 1987; **9**: 1210–2.

94 Takishita S, Muratani H, Kawazoe N, Kimura Y, Tozawa M, Fukiyama K. Neural effects on renal blood flow during acute hypertension vary with antihypertensive drugs. *Hypertension* 1994; **23**: 197–101.

95 Hamaya Y, Nishikawa T, Dohl S. Diuretic effect of clonidine during isoflurane, nitrous oxide, and oxygen anesthesia. *Anesthesiology* 1994; **81**: 811–9.

96 Smyth DD, Umemura S, Yang E, Pettinger WA. Inhibition of renin release by alpha-adrenoceptor stimulation in the isolated perfused rat kidney. *Eur J Pharmacol* 1987; **140**: 33–8.

97 Coffman JD, Cohen RA. Role of alpha-adrenoceptor subtypes mediating sympathetic vasoconstriction in human digits. *Eur J Clin Invest* 1988; **18**: 309–13.

98 Baker CH, Davis DL, Sutton ET. Blood flow distribution with adrenergic and histaminergic antagonists. *Proc Soc Exp Biol Med* 1989; **190**: 260–7.

99 Flavahan NA. The role of vascular alpha2-adrenoceptors as cutaneous thermosensors. *NIPS* 1991; **6**: 251–5.

100 Delaunay L, Bonnet F, Duvaldestin P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. *Br J Anaesth* 1991; **67**: 397–401.

101 Flacke J, Bloor B, Flacke W, *et al*. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

CHAPTER 3

Anesthetic effects of α_2-adrenergic receptor agonists - a review of the literature

During the past few years a whole range of beneficial effects of α_2-adrenergic agonists have been described, many of which are potentially useful in anesthesia. Below are listed the presently known effects of these agents.

Effects of α_2-adrenergic agonists:

sedation [1]
anxiolysis [2]
antisialogue [3]
cardiovascular stabilizing [4]
anesthetic sparing [4]
systemic analgesic [5]
anti-nausea, anti-emesis [6]
sympatholytic [7]
reduction in intra-ocular pressure [8]
epidural and spinal analgesia [9]
reduced intra-cranial pressure [10]
neuro-protection [11]
prevention of muscle rigidity [12]
reduction in post-operative shivering [13]
reduction in post-operative oxygen requirement [14]
treatment of alcohol withdrawal [15]
treatment of opiate withdrawal [16]

Many of these actions are of immediate interest in anesthetic practice and will be further discussed in this chapter.

3.1 Sedation and anxiolysis

Sedation has always been a problem for the use of clonidine and other α_2-adrenergic agonists as anti-hypertensives and the attempted seperation of sedative and anti-hypertensive effect has not proved entirely successful [17]. Belleville *et al.* studied

dexmedetomidine 0.25, 0.5, 1, and 2 μg/kg given intravenously to volunteers. They found that most patients who received 1 or 2 μg/kg dexmedetomidine were deeply sedated and unresponsive to stimuli, the sedation lasting for a mean of 195 min following the highest dose [1].

Low doses of α_2-adrenergic agonists possess anxiolytic properties in humans [2,18]. This has been confirmed in animal models of anxiety [19,20].

3.2 Reduction of anesthetic requirements

The central noradrenergic system has been shown to be an important mediator of the hypnotic actions of volatile anesthetics, anesthetic requirements being related to central noradrenaline levels [21]. Prior administration of central noradrenaline depletors (α-methyldopa and reserpine), reduced the minimal alveolar concentration (MAC) for halothane in dogs, while administration of central noradrenaline elevators (iproniazid) was associated with an increase in cyclopropane anesthetic requirements. Pretreatment with guanethidine, an agent which depletes peripheral, but not central, noradrenaline levels, was not associated with a change in anesthetic requirement [21]. Roizen *et al.* showed that halothane and cyclopropane both consistently and selectively altered neurotransmitter content in a small fraction of brain nuclei, the locus coeruleus, central grey catecholamine area and nucleus raphe dorsalis [22]. They further showed that destruction of these discrete areas caused reductions in anesthetic requirements in rats. Localized lesions of the locus coeruleus produced a similar change in halothane MAC as did the pharmacological destruction of the entire noradrenergic system [23]. Clonidine was shown to reduce halothane MAC in rats [24], and the more selective α_2-adrenergic agonist, azepexole, reduced halothane MAC by more than 85% [25], whereas disruption of noradrenergic pathways never caused a reduction of more than 40% in anesthetic requirements [21,23]. Rats, in which the central noradrenaline stores were almost totally depleted, have a lower basal MAC than normal rats, but dexmedetomidine could further reduce MAC for halothane [26]. Therefore, other mechanisms beside synaptic depletion of noradrenaline must be involved. The most likely site of this action is a postsynaptic α_2-adrenoceptor [27]. The sedative/hypnotic effects of α_2-agonists are currently believed to be mediated primarily by α_2-adrenoceptors in the locus coeruleus in the brain by reducing the firing rate of noradrenergic coerulocortical neurons [28–30].

3.3 Analgesia

α_2-Adrenergic agonists have been shown to produce analgesia by action at α_2-adrenergic receptors independent of the opiate receptors [31]. Their analgesic effects have been demonstrated in animals [32,33] and in man [5]. In contrast to opioids, the analgesia produced by α_2-agonists is not associated with respiratory depression [34,35]. The mechanisms of this analgetic action have not been fully elucidated. In the

locus coeruleus, common effector mechanisms have been found for both α_2-adrenergic and opioid systems [36].

Also, there is a spinal component of α_2-adrenoceptor-mediated analgesia which is independent of opioid receptor mechanisms [37,38], but which may react synergistically with the opioid receptors [39,40]. In a double-blind study in patients using self-administered epidural or intravenous clonidine, Bernard *et al.* showed that post-operative analgesia can be achieved by both routes. The epidural route was associated with significant reductions in self-administered clonidine dose, in plasma clonidine concentration, and in the level of sedation, indicating a clinically useful effect at the spinal level [41].

Eisenach *et al.* have shown that analgesia can spread upwards from the spinal segment where clonidine is injected when a continuous lumbar epidural infusion is given [42]. In this volunteer study he showed that it was possible to maintain a steady concentration of clonidine in the lumbar cerebro-spinal fluid (CSF) when a pharmacokinetically-designed, computer-controlled infusion of clonidine is given via the lumbar epidural space. Clonidine caused similar dose-related analgesia in both the foot and the hand, suggesting that continuous addition of clonidine to the lumbar CSF occurs allowing cephalad spread of the drug in the CSF.

In addition, oral clonidine has been shown to prolong sensory and motor block from lidocaine spinal anesthesia [43]. Thus, various mechanisms at several levels within the central nervous system seem to be involved in the analgesic actions of α_2-adrenergic agonists.

Epidural clonidine has also been studied in the management of patients with chronic cancer pain. In a randomized, double-blind study, clonidine has been shown to be effective for the treatment of intractable cancer pain, especially in patients with neuropathic pain [44].

3.4 Reduction in oxygen uptake and shivering

Clonidine has been shown to reduce oxygen uptake and carbon dioxide production in the post-operative period [13,14]. Some studies showed a decrease in the incidence of shivering after clonidine [13,45] while other studies could detect no difference between clonidine and placebo [14]. Reduction in post-operative shivering has also been reported for dexmedetomidine [46].

3.5 Anti-emetic effects

Clonidine premedication has been shown to reduce postoperative vomiting in children [47], although the mechanism is unknown. α_2-Adrenergic agonists are known to diminish salivary flow [48] and reduce gastro-intestinal motility [49], which may, in part, explain this effect.

3.6 Reduction in intra-ocular pressure

Both clonidine and dexmedetomidine have been shown to reduce intra-ocular pressure (IOP) [8,50]. Intravenous dexmedetomidine almost entirely prevented the increase in IOP after laryngoscopy and tracheal intubation [50]. In another ophthalmological study, intramuscular dexmedetomidine was given as premedication for outpatient cataract surgery under peri-ocular anesthesia [51]; dexmedetomidine 1 μg/kg given intramuscularly 60 min prior to surgery lowered IOP when compared to midazolam or placebo and provided a light sedative effect without compromising the cooperation of the patient.

3.7 The α_2-adrenergic agonists in anesthesia

α_2-Adrenergic agonists are commonly used as anesthetics in veterinary practice. Xylazine, the first α_2-adrenergic agonist to be used as veterinary sedative and analgesic, is widely used either alone or as an adjunct to ketamine anesthesia [52,53]. Detomidine shows a dose-dependent analgesia and sedative effect in horses and cattle. Medetomidine is used for sedation in dogs and non-domestic animals [54].

α_2-adrenergic agonists have been advocated for some time as adjuncts to general anesthesia in humans. Originally, clonidine was investigated in a variety of clinical settings, but was limited by the absence of an intravenous formulation in the U.S.A. Moreover, while clonidine can decrease volatile anesthetic requirements up to a maximum of 48% [55], the more α_2-selective adrenergic agonist, dexmedetomidine has been shown to reduce halothane anesthetic requirements by more than 90% in rats [26]. Therefore, we chose to study the safety and efficacy of dexmedetomidine in this thesis.

3.7.1 Clonidine

Clonidine has been investigated for its anesthetic-sparing and hemodynamic-stabilising effects in a number of clinical studies.

Flacke *et al.* gave patients undergoing coronary artery bypass grafting either placebo or clonidine (200 or 300 μg orally, based on patient weight) 90 min prior to arrival in the operating room, and a second dose via nasogastric tube while the patient was on cardiopulmonary bypass. Clonidine patients were more sedated on arrival in the operating room and required 40% less sufentanil during operation (as assessed by hemodynamic criteria). At all times the heart rate and blood pressure were significantly lower in the clonidine group; cardiac output was higher and systemic vascular resistance (SVR) lower following cardiopulmonary bypass. Plasma catecholamines were consistently lower in the treated group [45].

Ghignone *et al.* using electro-encephalogram (EEG) measurement of anesthetic depth (shift to 0.5–3 Hz frequency range) demonstrated a 45% reduction in fentanyl requirements following 5 μg/kg clonidine orally 90 min before arrival in the operating room [56]. In a further study, the hemodynamic response to endotracheal intubation in mildly hypertensive patients receiving either clonidine alone or a combination of diazepam and lidocaine was investigated. Preoperative blood pressure was better controlled and there was no tachycardic response to intubation in the clonidine group [57]. Using EEG as index of anesthetic depth Ghignone *et al.* demonstrated a reduction in volatile anesthetic requirement by 40% and in fentanyl requirement by 74%, while hemodynamic stability was better maintained. In a study of patients undergoing aortic surgery, clonidine 5 μg/kg 90 min prior to surgery reduced the requirements for alfentanyl and droperidol when compared to placebo. The clonidine-treated patients had fewer episodes of tachycardia and hypertension than the placebo group [58]. Clonidine has been shown to reduce the endocrine response to surgery and stabilise the cardiovascular response following aortic surgery [59].

3.7.2 *Dexmedetomidine*

In a single blind study, dexmedetomidine in four different doses (0.167, 0.33, 0.67, and 1.0 μg/kg) was given intravenously 15 min prior to induction of anesthesia for uterine dilatation and curettage. Thiopental was used for induction, and maintenance of anesthesia was with nitrous oxide/oxygen (70%/30%) supplemented with thiopental. The total amount of thiopental was reduced from 400 ± 166 mg (mean ± SD) after 0.167 μg/kg to 180 ± 65 mg after 1.0 μg/kg. Blood pressure, heart rate and noradrenaline levels were reduced after dexmedetomidine [60]. In a double blind study comparing dexmedetomidine (0.5, 1.0, and 1.5 μg/kg) with placebo given intramuscularly 60 min prior to induction, no difference was found in anesthetic requirements, but hemodynamic and sedative effects of dexmedetomidine were still apparent four hours after administration of the drug [61]. In a double-blind, randomised study of patients undergoing abdominal hysterectomy, a single intravenous dose of dexmedetomidine 0.6 μg/kg, given before the induction of anesthesia, reduced the increase in heart rate in response to tracheal intubation and diminished isoflurane requirements, when compared to that required by patients receiving fentanyl 2 μg/kg [4]. In a further study of patients undergoing abdominal hysterectomy, these authors investigated the effect of a two step infusion to rapidly achieve a steady state plasma concentration on anesthetic requirement. Dexmedetomidine infusion did not completely abolish the need for isoflurane but diminished its requirement by > 90%, while the heart rate response to tracheal intubation was considerably blunted [62].

References

1 Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992; **77**: 1125–33.

2 Redmond D. Does clonidine alter anxiety in humans? *Trends Pharmacol Sci* 1982; **3**: 477–80.

3 Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine–a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; **13**: 635–51.

4 Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; **74**: 997–1002.

5 Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Korttila KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991; **73**: 112–8.

6 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5.

7 Kallio A, Scheinin M, Koulu M, *et al.* Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. *Clin Pharmacol Ther* 1989; **46**: 33–42.

8 Ghignone M, Noe C, Calvillo O, Quintin L. Anesthesia for ophthalmic surgery in elderly: the effects of clonidine on intra-ocular pressure, perioperative hemodynamics, and anesthetic requirement. *Anesthesiology* 1988; **68**: 707–16.

9 Kalso EA, Poyhia R, Rosenberg PH. Spinal antinociception by dexmedetomidine, a highly selective alpha 2-adrenergic agonist. *Pharmacol Toxicol* 1991; **68**: 140–3.

10 Zornow MH, Scheller MS, Sheehan PB, Strnat MA, Matsumoto M. Intracranial pressure effects of dexmedetomidine in rabbits. *Anesth Analg* 1992; **75**: 232–7.

11 Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Reversal by the alpha 2-adrenergic antagonist atipamezole. *Anesthesiology* 1991; **75**: 328–32.

12 Weinger MB, Segal IS, Maze M. Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. *Anesthesiology* 1989; **71**: 242–9.

13 Delaunay L, Bonnet F, Duvaldestin P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. *Br J Anaesth* 1991; **67**: 397–401.

14 Quintin L, Viale JP, Annat G, *et al.* Oxygen uptake after major abdominal surgery: effect of clonidine. *Anesthesiology* 1991; **74**: 236–41.

15 Wilkins AJ, Jenkins WJ, Steiner JA. Efficacy of clonidine in treatment of alcohol withdrawal state. *Psychopharmacology* 1983; **81**: 78–80.

16 Gold MS, Pottash AC, Sweeney DR, Klever HD. Opiate withdrawal using clonidine. A safe, effective, and rapid nonopiate treatment. *JAMA* 1980; **243**: 343–6.

17 van Zwieten PA. Drugs interacting with alpha adrenoceptors. *Cardiovasc Drugs Ther* 1989; **3**: 121–33.

18 Hoehn-Saric R, Merchant A, Keyser M, Smith V. Effects of clonidine on anxiety disorders. *Arch Gen Psychiatry* 1981; **38**: 1278–82.

19 Lammintausta R, Uyeno E, Hollister L, Csernansky J. A selective alpha-2-agonist, medetomidine, shows anxiolytic effects in the rat approach/avoidance conflict test., ACNP Abstracts. Washinton DC, 1986, pp 205.

20 Handley S, Mithani S. Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour. *Naunyn-Schmiedebergs Arch Pharmacol* 1984; **327**: 1–5.

21 Miller RD, Way WL, Eger EI. The efects of alpha-methyldopa, reserpine, guanethidine and iproniazid on minimum alveolar anesthetic requirement (MAC). *Anesthesiology* 1968; **29**: 1153–8.

22 Roizen M, Kopin I, Thoa N, *et al*. The effect of two anesthetic agents on norepinephrine and dopamine in discrete brain nuclei, fiber tracts and terminal regions of the rat. *Brain Res* 1976; **110**: 515–22.

23 Roizen MF, White PF, Eger EI, Brownstein M. Effects of ablation of serotonin or norepinephrine brain-stem areas on halothane and cyclopropane MACs in rats. *Anesthesiology* 1978; **49**: 252–5.

24 Maze M, Birch B, Vickery R. Clonidine reduces halothane MAC in rats. *Anesthesiology* 1987; **67**: 868–9.

25 Maze M, Vickery R, Merlone S, Gaba D. Anesthetic and hemodynamic effects of the alpha$_2$-adrenergic agonist, azepexole, in isoflurane anesthetized dogs. *Anesthesiology* 1988; **68**: 689–94.

26 Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. *Anesthesiology* 1988; **69**: 818–23.

27 Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology* 1989; **71**: 75–9.

28 Cedarbaum JM, Aghajanian GK. Catecholamine receptors on locus coeruleus neurons: pharmacological characterization. *Eur J Pharmacol* 1977; **44**: 375–85.

29 DeSarro GB, Ascioti C, Froio F, Libri V, Nistico G. Evidence that locus coeruleus is the site where clonidine and drugs acting at α_1- and α_2-adrenoceptors affect sleep and arousal mechanisms. *Br J Pharmacol* 1987; **90**: 675–85.

30 Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats [see comments]. *Anesthesiology* 1992; **76**: 948–52.

31 Spaulding TC, Fielding S, Venafro JJ, Lal H. Antinocioceptive activity of clonidine and its potentiation of morphine analgesia. *Eur J Pharmacol* 1979; **58**: 19–25.

32 Puke MJ, Wiesenfeld HZ. The differential effects of morphine and the alpha 2-adrenoceptor agonists clonidine and dexmedetomidine on the prevention and treatment of experimental neuropathic pain. *Anesth Analg* 1993; **77**: 104–9.

33 Ylisela E, Vainio O. Effects of medetomidine on the experimental auricular pain in dogs. *Acta Vet Scand Suppl* 1989; **85**: 187–91.

34 Furst SR, Weinger MB. Dexmedetomidine, a selective alpha 2-agonist, does not potentiate the cardiorespiratory depression of alfentanil in the rat. *Anesthesiology* 1990; **72**: 882–8.

35 Bailey PL, Sperry RJ, Johnson GK, *et al*. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology* 1991; **74**: 43–8.

36 Aghajanian G, Wang Y. Common α_2-opiate and effector mechanisms in the locus coeruleaus: intracellular studies in brain slices. *Neuropharmacology* 1987; **26**: 793–9.

37 Solomon RE, Brody MJ, Gebhart GF. Pharmacological characterization of alpha adrenoceptors involved in the antinociceptive and cardiovascular effects of intrathecally administered clonidine. *J Pharmacol Exp Ther* 1989; **251**: 27–38.

38 Ossipov MH, Harris S, Lloyd P, Messineo E, Lin BS, Bagley J. Antinociceptive interaction between opioids and medetomidine: systemic additivity and spinal synergy. *Anesthesiology* 1990; **73**: 1227–35.

39 Sullivan AF, Kalso EA, McQuay HJ, Dickenson AH. Evidence for the involvement of the mu but not delta opioid receptor subtype in the synergistic interaction between opioid and alpha 2 adrenergic antinociception in the rat spinal cord. *Neurosci Lett* 1992; **139**: 65–8.

40 Sullivan AF, Kalso EA, McQuay HJ, Dickenson AH. The antinociceptive actions of dexmedetomidine on dorsal horn neuronal responses in the anaesthetized rat. *Eur J Pharmacol* 1992; **215**: 127–33.

41 Bernard JM, Kick O, Bonnet F. Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia. *Anesth Analg* 1995; **81**: 706–12.

42 Eisenach JC, Hood DD, Tuttle R, Shafer S, Smith T, Tong CH. Computor-controlled epidural infusion to targeted cerebrospinal fluid concentrations in humans. Clonidine. *Anesthesiology* 1995; **83**: 33–47.

43 Liu S, Chiu A, Neal J, Carpenter R, Bainton BG, Gerancher JC. Oral clonidine prolongs lidocaine spinal anesthesia in human volunteers. *Anesthesiology* 1995; **82**: 1353–9.

44 Eisenach JC, Du Pen S, Dubois M, Miguel R, Allin D. Epidural clonidine for intractable cancer pain. *Pain* 1995; **61**: 391–9.

45 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

46 Erkola O, Korttila K, Aho M, Haasio J, Aantaa R, Kallio A. Comparison of intramuscular dexmedetomidine and midazolam premedication for elective abdominal hysterectomy. *Anesth Analg* 1994; **79**: 646–53.

47 Mikawa K, Nishina K, Maekawa N, Asano M, Obara H. Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42**: 977–81.

48 Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha 2-adrenoceptor agonist effects by atipamezole in human volunteers. *Br J Clin Pharmacol* 1991; **31**: 160–5.

49 Wikberg J. Localization of adrenergic receptors in guinea pig ileum and rabbit jejunum to cholinergic neurons and to smooth muscle cells. *Acta Physiol Scand* 1977; **99**: 190–207.

50 Jaakola ML, Ali MT, Kanto J, Kallio A, Scheinin H, Scheinin M. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. *Br J Anaesth* 1992; **68**: 570–5.

51 Virkkila M, Ali MT, Kanto J, Turunen J, Scheinin H. Dexmedetomidine as intramuscular premedication for day-case cataract surgery. A comparative study of dexmedetomidine, midazolam and placebo. *Anaesthesia* 1994; **49**: 853–8.

52 Moens Y, Fargetton X. A comparative study of medetomidine/ketamine and xylazine/ketamine anaesthesia in dogs [see comments]. *Vet Rec* 1990; **127**: 567–71.

53 Verstegen J, Fargetton X, Donnay I, Ectors F. Comparison of the clinical utility of medetomidine/ketamine and xylazine/ketamine combinations for the ovariectomy of cats. *Vet Rec* 1990; **127**: 424–6.

54 MacDonald E, Scheinin H, Scheinin M. Behavioural and neurochemical effects of medetomidine, a novel veterinary sedative. Eur J Pharmacol 1988; **158**: 119–27.

55 Kaukinen S, Pyykkö K. The potentiation of halothane anaesthesia by clonidine. *Acta Anaesthesiol Scand* 1979; **23**: 107–11.

56 Ghignone M, Quintin L, Duke P, Kehler C, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.

57 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.

58 Engelman E, Lipszyc M, Gilbart E, *et al.* Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–87.

59 Quintin L, Roudot F, Roux C, *et al.* Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *Br J Anaesth* 1991; **66**: 108–15.

60 Aantaa RE, Kanto JH, Scheinin M, Kallio AM, Scheinin H. Dexmedetomidine premedication for minor gynecologic surgery. *Anesth Analg* 1990; **70**: 407–13.

61 Aantaa R, Kanto J, Scheinin M. Intramuscular dexmedetomidine, a novel alpha 2-adrenoceptor agonist, as premedication for minor gynaecological surgery. *Acta Anaesthesiol Scand* 1991; **35**: 283–8.

62 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992; **75**: 940–6.

CHAPTER 4

Comparison of the hemodynamic and coronary vascular effects of dexmedetomidine and clonidine in the anesthetized dog†

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The hemodynamic and coronary vascular effects of the new selective α_2-adrenergic agonist dexmedetomidine and the established but less α_2-selective agonist clonidine have not yet been compared in the same protocol in vivo. To this purpose we studied 15 anesthetized open-chest dogs. After baseline measurements, seven dogs received dexmedetomidine in doses of 0.1, 0.3, 1, 3, and 10 μg/kg and eight dogs were given clonidine 1, 3, 10, and 30 μg/kg as 2-min intravenous injections at 20-min intervals. Two minutes after drug administration dexmedetomidine was 3–10 times more potent than clonidine in increasing blood pressure and systemic and coronary vascular resistance and decreasing heart rate, cardiac output, and mixed venous and coronary venous oxygen saturation. Within 15 min the pressor effect faded and both venous oxygen saturations recovered for dexmedetomidine and clonidine. High dose clonidine (10 and 30 μg/kg) induced prolonged coronary vasoconstriction and reduction in dP/dt_{max}. We conclude that slow administration is more important for the potent and selective α_2-adrenergic agonist dexmedetomidine than for clonidine. Dexmedetomidine lacks the untoward, probably α_1-adrenergic effects, occurring at high doses of clonidine.

Introduction

α_2-Adrenergic agonists have a number of central nervous system actions which may be beneficially applied in clinical anesthesia; those reported include sedation, anxiolysis, analgesia, reduction of anesthesia requirement, and a reduction of the hemodynamic and metabolic stress response to anesthesia and surgery [1]. Clonidine, one of the first α_2-adrenergic agonists used clinically, reduced the minimal alveolar

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concentration (MAC) for halothane by 40%–50%, in dogs [2] and rats [3] but a ceiling effect was noted so that increasing the dose tenfold did not further reduce anesthetic requirements. This is thought to be due to α_1-adrenergic receptor activation by high doses of clonidine antagonizing the α_2-adrenergic receptor mediated hypnotic response. Dexmedetomidine is one of the newer generation of α_2-adrenergic agonist with a greater selectivity for the α_2-adrenergic receptor [4] and a greater anesthetic-sparing effect than clonidine [5,6]. Dexmedetomidine is the dextro enantiomer of medetomidine, the laevo enantiomer being inactive [7,8]. Medetomidine is routinely used in veterinary anesthesia. Volunteer and clinical studies have shown dexmedetomidine's sedative, anxiolytic, analgesic and anesthetic agent sparing actions in man [9,10].

Besides these sedative effects, α_2-adrenergic agonist have also considerable hemodynamic effects. They are known to give rise to a rapid pressor effect followed by a long lasting reduction in heart rate and blood pressure. This has been demonstrated for both drugs [11–16], but never compared in the same experimental setting. Of special interest is the effect on the coronary circulation, since some reports suggest that α_2-adrenergic mediated coronary vasoconstriction may occur [17].

Therefore we studied dexmedetomidine and clonidine in a dog model, which allowed extensive measurements of hemodynamic and coronary vasculat variables. Since the dog is more prone to α_2-adrenergic vasoconstriction than man [13], possibly harmful vasoconstrictive effects can be determined more sensitively in this species.

Methods

These experiments conformed to the Dutch law for animal experimentation, and were approved by the local animal ethical committee. Fifteen adult, healthy, mongrel dogs of either sex weighing between 20 and 40 kg were fasted overnight then premedicated with fentanyl 250 μg intramuscularly 30 min prior to anesthesic induction. Anesthesia was induced with thiopental 20 mg/kg intravenously given via a vein in the hind leg. After intubation, the dogs were ventilated with a mixture of oxygen 40% and nitrous oxide 60% using a Drager Pulmomat mechanical ventilator. Tidal volume (initially 15 mL/kg) and respiratory rate (12–18 per min) were adjusted to maintain end-expired carbon dioxide concentration (Datex capnograph Oscar, Datex Instrumentation Corp., Helsinki, Finland) between 3.5 and 4.5 kPa. Halothane 1.0% was added to the inspired gases. Fentanyl 1–2 μg/kg intravenously was given as necessary to maintain heart rate between 90 and 110 bpm. Oxygen saturation was monitored by tongue pulse oximetry (Datex Oscar) and arterial blood gases were analyzed every half hour during the study (ABL 3, Radiometer). Arterial desaturation was treated by increasing the inspiratory oxygen concentration and metabolic acidosis by infusing sodium bicarbonate 4.2%. The temperature was recorded and maintained as close as possible to 38°C by means of a heating pad under the dog. A venous cannula was inserted in a leg vein for infusion of fluids and medication. Crystalloid (0.9% sodium chloride solution) was

infused to maintain hydration and replace losses. Colloid (Haemaccel, Behring Pharma) was infused to replace blood loss. A femoral artery was surgically exposed and a long catheter for arterial blood sampling and measurement of arterial pressure (Millar micro-manometer catheter tip) introduced into the aorta. The thorax was opened via the fifth lateral intercostal space and the pericardium opened to expose the heart. The left interventricular coronary artery was prepared and a flow probe (Skalar, Delft, The Netherlands) placed around it near its origin. A small polyethelene catheter (PE 60) was inserted into the coronary vein accompanying the artery in order to obtain regional venous blood samples. A micro-manometer cathetertip transducer (Millar, Housten, TX, U.S.A.) was inserted into the left ventricle via the left common carotid artery or the right femoral artery. The first positive derivative of left ventricular pressure ($LVdP/dt_{max}$) and heart rate were derived from the left ventricular pressure signal. A thermodilution pulmonary artery catheter was introduced via the left external jugular vein and floated into the pulmonary artery using the continuously displayed pressure tracing as a guide. This catheter was used to obtain mixed venous blood samples from the pulmonary artery and to measure cardiac output by the thermodilution technique using a cardiac output computer (Edwards SAT 1). Cardiac output was measured in triplicate using cold injectate and the average taken. Left ventricular pressure, aortic pressure, coronary flow and electrocardiogram (lead II) were displayed continuously (Knott). All pressures and flows were recorded continuously using a Schwarzer pen-recorder at 0.25 cm/s, increased to 5 cm/s during data acquisition.

Dexmedetomidine was supplied by Orion Corp., Farmos, Turku, Finland as a crystalline powder. This was disolved in saline to produce a solution containing 100 μg/kg. The calculated dose was taken from this solution and diluted to 20 mL in saline before injection. Clonidine (Sigma Chemical Corp., St Louis, MO, U.S.A.) was supplied as a crystalline powder. This was dissolved in saline to produce a solution containing 100 μg/kg. The calculated dose was taken from this solution and diluted to 20 mL in saline before injection. All test medications were given over two minutes into the right atrium through the right atrial port of the pulmonary artery catheter.

After a stabilization period of 30 min baseline measurements were taken. Following this, increasing doses of clonidine or dexmedetomidine were given as stated above and measurements recorded at peak blood pressure effect (within 1–2 min), and 15 min later. Eight dogs received clonidine in the doses 1, 3, 10, and 30 μg/kg and seven dogs dexmedetomidine in the doses 0.1, 0.3, 1, 3, and 10 μg/kg at 20-min intervals.

At each measurement point the following data were obtained: heart rate, mean arterial pressure, left ventricular end-diastolic pressure, coronary flow, $LVdP/dt_{max}$, thermodilution cardiac output; arterial, mixed venous (pulmonary artery) and coronary venous blood was collected for measurement of hemoglobin and blood gases. (ABL 3, Radiometer blood gas analyzer, OSM 2 hemoximeter (Radiometer) saturation analyzer (calibrated for dog blood)).

Systemic vascular resistance (SVR), and coronary vascular resistance (CVR) were calculated using the formulae below:

$$SVR = MAP \times 80 / CO \ (dynes \cdot s \cdot cm^{-5})$$

where

MAP = mean arterial pressure (mm Hg)
CO = cardiac output (L/min)

$$CVR = MAP / CF \ (mm\ Hg \cdot mL^{-1} \cdot min^{-1})$$

where CF = coronary blood flow (mL/min).

Statistical analysis

Two-way analysis of variance for repeated measures was used for intergroup comparisons. Intragroup comparisons were evaluated using one-way analysis of variance for repeated measures. When significance was found, Fisher's protected least significant difference test was used as a *post-hoc* multiple comparison procedure. Baseline values between the two groups were compared using Student's *t*-test. A *P* value of less than 0.05 was considered significant.

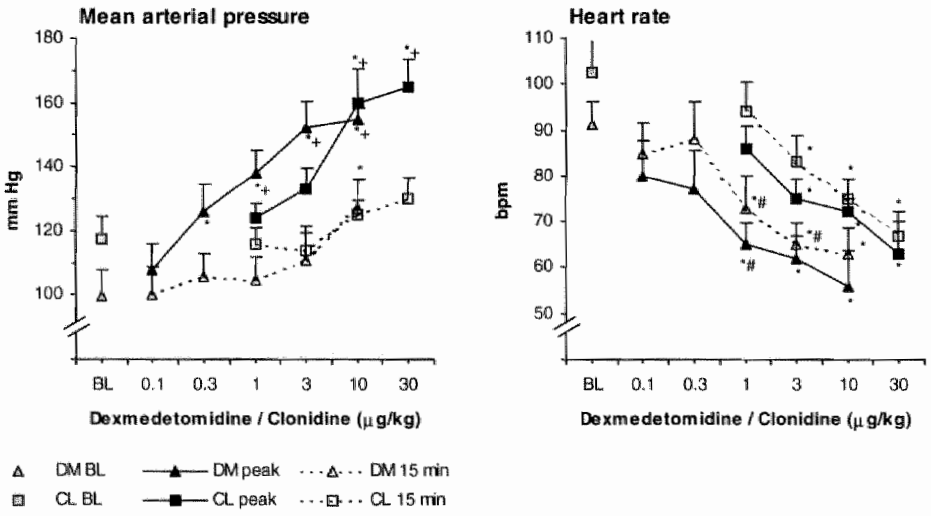

Figure 4-1 Effects of dexmedetomidine (DM) and clonidine (CL) on mean arterial pressure (left) and heart rate (right). Measurements at baseline (BL), peak mean arterial blood pressure (peak), and 15 min after administration (15 min). All values are mean ± SEM. * Significantly different from baseline. # Significant difference between the two groups. + Significant difference between peak and 15-min value.

Results

Figure 4-1 depicts the effect of the two drugs on mean arterial pressure. Increasing doses of the drugs caused increasingly high peaks in mean arterial pressure. Fifteen minutes after 'peak' effect, MAP was only increased after 10 μg/kg dexmedetomidine. Two minutes after administration of dexmedetomidine blood pressure increased more than after the same dose of clonidine. However, 15 min later there was no significant difference in the change in blood pressure (Figure 4-1). Heart rate decreased significantly after dexmedetomidine ≥1 μg/kg and after clonidine ≥3 μg/kg. The effect was dose-dependent both for peak and 15-min values and there was no significant difference between peak and 15-min values (Figure 4-1).

Both drugs decreased cardiac output dose-dependently (Figure 4-2). This reduction was significant for dexmedetomidine ≥1 μg/kg and clonidine ≥10 μg/kg. No significant recovery of cardiac output occurred within 15 min with either drug (Figure 4-2). Both α_2-agonists dose-dependently increased systemic vascular resistance. Two minutes after drug administration this increase was significant for dexmedetomidine ≥1 μg/kg and for clonidine ≥10 μg/kg (Figure 4-2). Systemic vascular resistance recovered to baseline values after dexmedetomidine 1 μg/kg but not after clonidine 10 μg/kg (Figure 4-2).

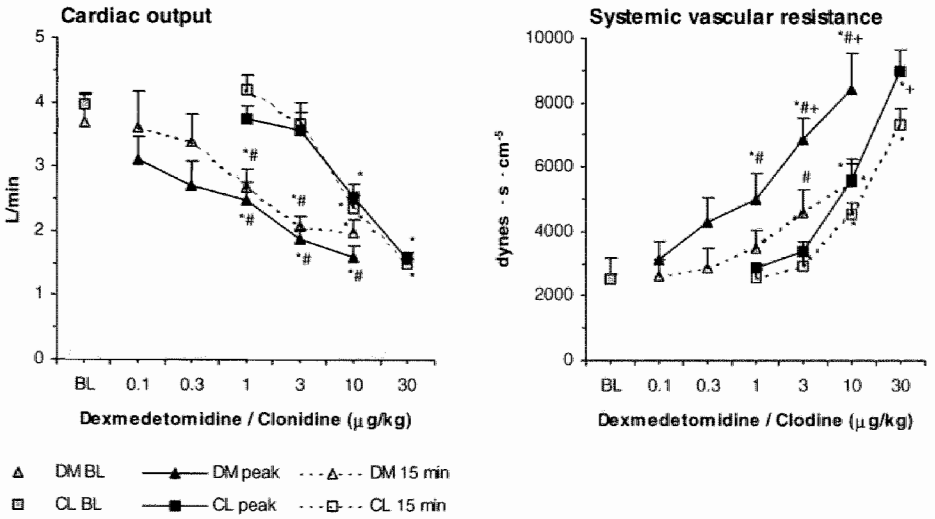

Figure 4-2 Effects of dexmedetomidine (DM) and clonidine (CL) on cardiac output (left) and systemic vascular resistance (right). Measurements at baseline (BL), peak mean arterial blood pressure (peak), and 15 min after administration (15 min). All values are mean ± SEM. * Significantly different from baseline. # Significant difference between the two groups. + Significant difference between peak and 15-min value.

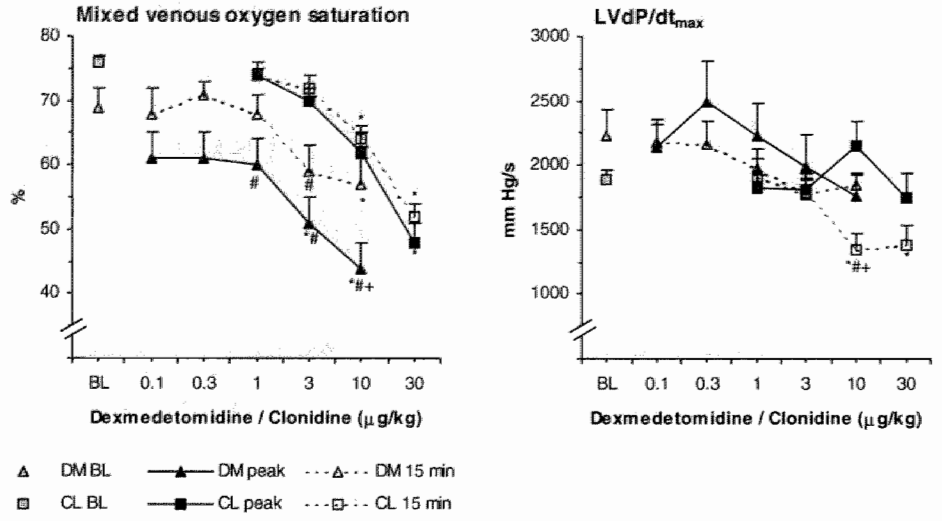

Figure 4-3 Effects of dexmedetomidine (DM) and clonidine (CL) on mixed venous oxygen saturation (left) and $LVdP/dt_{max}$ (right). Measurements at baseline (BL), peak mean arterial blood pressure (peak), and 15 min after administration (15 min). All values are mean ± SEM. * Significantly different from baseline. # Significant difference between the two groups. + Significant difference between peak and 15-min value.

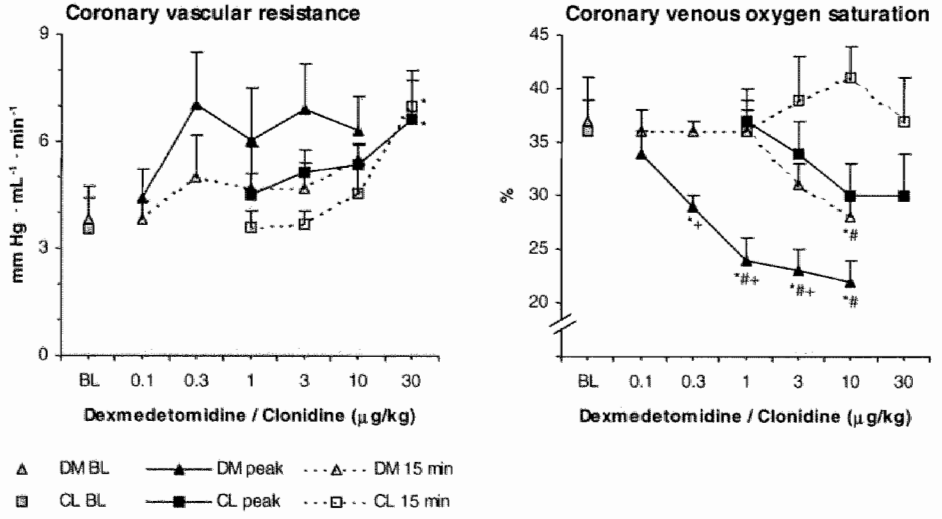

Figure 4-4 Effects of dexmedetomidine (DM) and clonidine (CL) on coronary vascular resistance (left) and coronary venous oxygen saturation (right). Measurements at baseline (BL), peak mean arterial blood pressure (peak), and 15 min after administration (15 min). All values are mean ± SEM. * Significantly different from baseline. # Significant difference between the two groups. + Significant difference between peak and 15-min value.

Table 4-1 Effects of increasing doses of dexmedetomidine or clonidine

Variable	Dose	Baseline	0.1 μg/kg		0.3 μg/kg		1.0 μg/kg	
			peak	15 min	peak	15 min	peak	15 min
SV	DM	40.7 ± 4.6	38.3 ± 2.5	42.8 ± 5.5	35.4 ± 4.0	38.7 ± 3.9	41.4 ± 7.7	37.6 ± 4.0
(mL)	CL	38.0 ± 1.9					41.4 ± 2.6	41.7 ± 3.2
LVEDP	DM	8.2 ± 2.6	7.9 ± 0.1	7.4 ± 0.1	9.9 ± 0.1	7.6 ± 0.1	15.9 ± 2.8*	8.4 ± 2.9
(mm Hg)	CL	10.6 ± 1.0					11.5 ± 1.2	11.8 ± 1.0
CF	DM	33.3 ± 5.6	29.6 ± 4.5	28.4 ± 3.1	22.8 ± 3.9	26.7 ± 4.1	28.3 ± 3.8	27.2 ± 3.1
(mL/min)	CL	36.4 ± 3.9					31.4 ± 4.2	36.3 ± 4.3

		3.0 μg/kg		10 μg/kg		30 μg/kg	
		peak	15 min	peak	15 min	peak	15 min
SV	DM	31.3 ± 4.1†	32.7 ± 2.9	30.4 ± 4.9	32.9 ± 4.0		
(mL)	CL	44.8 ± 4.2†	41.6 ± 4.5	33.5 ± 2.8	31.5 ± 2.4	25.7 ± 2.5*	22.8 ± 2.2*
LVEDP	DM	16.7 ± 3.1*	9.9 ± 3.0	18.6 ± 2.3*	11.0 ± 2.2		
(mm Hg)	CL	14.8 ± 1.5	12.1 ± 1.3	19.0 ± 2.6*	12.1 ± 1.6	19.0 ± 2.0*	11.5 ± 2.0
CF	DM	29.0 ± 6.3	27.6 ± 4.0	29.6 ± 5.2	23.6 ± 1.7		
(mL/min)	CL	30.1 ± 4.6	34.4 ± 4.2	31.9 ± 3.4	33.6 ± 5.0	30.8 ± 5.6	22.1 ± 3.5*

Values are expressed as mean ± SEM. peak = peak blood pressure effect; 15 min = effect 15 min after peak effect; SV = stroke volume; LVEDP = left ventricular end-diastolic pressure; CF = coronary blood flow; DM = dexmedetomidine; CL = clonidine; SEM = standard error of the mean. * Significantly different from baseline. † Significant difference between DM and CL.

In both groups the immediate changes in mixed venous oxygen saturation followed the changes in cardiac output. (Figure 4-3). After dexmedetomidine 10 μg/kg mixed venous saturation recovered significantly while after clonidine 10 and 30 μg/kg there was no significant recovery. $LVdP/dt_{max}$ was not significantly altered by even the highest doses of dexmedetomidine (Figure 4-3). In contrast, clonidine (10 and 30 μg/kg) decreased $LVdP/dt_{max}$ 15 min after administration, although not at peak effect.

Dexmedetomidine did not significantly affect stroke volume, but 30 μg/kg clonidine caused a significant decrease in stroke volume (Table 4-1). Left ventricular end-diastolic pressure increased significantly after dexmedetomidine ≥1 μg/kg and clonidine ≥10 μg/kg but recovered after 15 min with all doses (Table 4-1). No significant changes occurred in coronary blood flow after either drug except 15 min after clonidine 30 μg/kg (Table 4-1).

At low doses clonidine affected coronary vascular resistance less than dexmedetomidine, but after 30 μg/kg a pronounced, significant increase in coronary vascular resistance occurred which did not decrease within 15 min (Figure 4-4). Coronary venous oxygen saturation decreased with increasing doses of dexmedetomidine above 0.3 μg/kg with significant recovery within 15 min after all doses except 10 μg/kg (Figure 4-4). No significant reduction in coronary venous oxygen saturation was seen after clonidine.

Table 4-2 Lowest dose with a statistically significant change from baseline

Variable	Dexmedetomidine (μg/kg)		Clonidine (μg/kg)	
	peak	15 min	peak	15 min
Heart rate	1	1	3	3
MAP	0.3	10	10	None
SVR	1	10	10	10
CVR	None	None	30	30
$MixvO_2$	3	10	10	10
$CorvO_2$	0.3	10	None	None
LVEDP	1	None	10	None
CO	1	1	10	10

peak = at peak effect; 15 min = 15 min after maximum effect; MAP = mean arterial pressure; SVR = systemic vascular resistance; CVR = coronary vascular resistance; $MixvO_2$ = mixed venous oxygen saturation; $CorvO_2$ = coronary venous oxygen saturation; LVEDP = left ventricular end diastolic pressure; CO = cardiac output.

Table 4-2 summarizes the lowest doses at which a significant change from baseline occurred for the variables shown.

Discussion

This study is the first to compare the systemic and coronary hemodynamic effects of clonidine and dexmedetomidine under the same conditions *in vivo*.

Peripheral vascular effects

The observation that changes in mean arterial pressure and cardiac output after dexmedetomidine 1 μg/kg were comparable to those after clonidine at doses between 3 and 10 μg/kg indicate dexmedetomidine's higher potency. These findings are in agreement with those of Kallio *et al.* in human volunteers, who showed a similar reduction in cardiac output and blood pressure for 100 μg medetomidine (the racemic mixture of dexmedetomidine and the biologically inactive L-medetomidine) and 200 μg clonidine [18]. The higher potency of dexmedetomidine is probably related to its higher selectivity for α_2-adrenergic receptors than clonidine, and the fact that dexmedetomidine is a full agonist at the α_2-adrenergic receptor whereas clonidine is a partial agonist [19].

A transient increase in blood pressure has also been reported after intravenous administration of clonidine and dexmedetomidine in man [20] and in dogs [15,16]. Such a transient pressure effect was not found after slower intravenous infusion in human volunteers [18] or oral administration in dogs [21].

The reason for the shorter lived vasoconstrictive effect of dexmedetomidine compared to clonidine may be related to its increased lipophilicity [22]. As a consequence, this drug is more rapidly distributed in a large volume and has easy access to the central

nervous system. The subsequent more powerful stimulation of central α_2-adrenergic receptors could cause sympatholysis and thus decrease of vasoconstriction.

Although dexmedetomidine has a shorter elimination half-life than clonidine [23] this is unlikely to be a contributing factor since the reduction in cardiac output and heart rate have been shown to persist for at least one hour after intravenous administration of 5 μg/kg in dogs [7], and for four hours following 20 μg/kg intravenously in dogs [11].

The more persistent vasoconstrictive effects of clonidine 10 and 30 μg/kg may be due to the fact that at these doses α_1-adrenergic effects are more apparent. Thus direct stimulation of α_1-adrenergic receptors in vascular smooth muscle may sustain vasoconstriction at high doses [24]. It is important to note that these effects occurred at doses of clonidine 2–6 times higher than used in clinical anesthesia.

Coronary vascular effects

The coronary vascular effects of clonidine and dexmedetomidine were less pronounced than the effects on the peripheral circulation. As for the peripheral vascular effects, dexmedetomidine was more potent than clonidine, but the coronary vascular effects were also short-lived except after the highest dose (10 μg/kg). It is well known that a considerable species difference exists in the sensitivity of the coronary vascular bed for α-adrenergic vasoconstriction, the dog being a species very prone to it [13]; a direct effect on isolated coronary artery strips has been demonstrated [25]. Recently, it has been shown by Indolfi *et al.* that α_2-adrenergic mediated increase in coronary vascular resistance in humans is 28% at most [26], a value less than half the maximum observed in the present study.

After a dose of 30 μg/kg clonidine a pronounced and prolonged coronary vasoconstriction was observed. As for the peripheral circulation, this might be due to the prevailing α_1-adrenergic effects.

Cardiac effects

A similar dose-dependent, cumulative and persistent bradycardia was found for clonidine (≥3 μg/kg) and dexmedetomidine (≥1 μg/kg). This bradycardic effect of α_2-adrenergic receptors is well known [27,28] and thought to be due to a combination of presynaptic inhibition of norepinephrine release at cardiac sympathetic nerve terminals and central reduction of sympathetic drive plus vagal facilitation of the baroreceptor reflex. A reduction in heart rate at constant venous return would result in an increase in end-diastolic volume and, due to the Frank-Starling mechanism, in a larger stroke volume. The absence of an increase in stroke volume as well as the tendency to a decrease in $LVdP/dt_{max}$ indicate a decrease in contractility.

Such a negative inotropic effect has been previously demonstrated for dexmedetomidine [11,12] and clonidine [16], and may be related to a reduction in central sympathetic outflow by stimulation of central α_2-adrenergic receptors [29]. Other studies have shown a reduction in plasma noradrenaline, supporting such sympatholytic effects [21,30,31].

Possible clinical relevance

Clonidine has been used clinically for 25 years in the treatment of hypertension [32], congestive heart failure [33] and to reduce myocardial ischemia and infarct size [34–36]. Moreover, clonidine in doses between 5 and 7 μg/kg reduced the hemodynamic response to tracheal intubation [37], stabilized hemodynamics during coronary artery bypass grafting [38], major vascular [39] and general surgery [40] without any obvious deleterious effects on myocardial function and reduced the metabolic response to anesthesia and surgery [41].

Dexmedetomidine has greater anesthetic-sparing effects then clonidine in animals [5] and humans [42], and in clinical studies has significant sedative [43] and analgesic [44] activity at doses of 0.5 to 1.5 μg/kg. It may, therefore, have advantages over clonidine when used as an anesthetic adjuvant.

In the present study performed in a species which is prone to α_2-adrenergic vasoconstriction [13] we found no evidence of prolonged vasoconstrictive effects after dexmedetomidine at a dose (0.5–2 μg/kg) likely to be used in humans.

Conclusion

In an animal model prone to α_2-adrenergic vasoconstriction, the hemodynamic effects of clonidine and dexmedetomidine are qualitatively similar, dexmedetomidine being 3–10 times more potent for the transient systemic and coronary vasoconstrictive effects. Fifteen minutes after administration the vasoconstrictive effects of dexmedetomidine are not greater than those of clonidine. At supraclinical doses clonidine has a more pronounced vasoconstrictive effect. These data indicate that slow intravenous administration is more important for a selective α_2-adrenergic agonist like dexmedetomidine than for the less selective clonidine and that dexmedetomidine lacks the possibly untoward α_1-adrenergic effects which occur at high doses of clonidine.

Acknowledgments

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References

1 Maze M, Tranquilli W. Alpha-2 Adrenoceptor Agonists: Defining the Role in Clinical Anesthesia. *Anesthesiology* 1991; **74**: 581–605.

2 Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg* 1982; **61**: 741–5.

3 Maze M, Birch B, Vickery R. Clonidine reduces halothane MAC in rats. *Anesthesiology* 1987; **67**: 868–9.

4 Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. *Eur J Pharmacol* 1988; **150**: 9–14.

5 Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. *Anesthesiology* 1988; **69**: 818–23.

6 Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha 2-adrenergic agonist, in halothane-anesthetized dogs. *Anesth Analg* 1988; **67**: 611–5.

7 Schmeling WT, Kampine JP, Roerig DL, Warltier DC. The effects of the stereoisomers of the alpha 2-adrenergic agonist medetomidine on systemic and coronary hemodynamics in conscious dogs. *Anesthesiology* 1991; **75**: 499–511.

8 Savola JM, Virtanen R. Central alpha 2-adrenoceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. *Eur J Pharmacol* 1991; **195**: 193–9.

9 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5.

10 Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; **74**: 997–1002.

11 Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M. Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992; **263**: 690–7.

12 Flacke WE, Flacke JW, Bloor BC, McIntee DF, Sagan M. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7**: 41–9.

13 Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation* 1990; **81**: 1–13.

14 Holtz J, Saeed M, Sommer O. Norepinephrine constricts the canine coronary bed via postsynaptic alpha$_2$-adrenoceptors. *Eur J Pharmacol* 1982; **82**: 199–202.

15 Jarvensivu P, Timisjarvi J, Kettunen R. The responses of the systemic and pulmonary circulations to intravenously administered clonidine in anaesthetized dogs. *Acta Physiol Scand Suppl* 1984; **537**: 23–30.

16 Timisjarvi J, Jarvensivu P, Kettunen R. Left ventricular responses to intravenous administration of clonidine in anaesthetized dogs. *Acta Physiol Scand Suppl* 1984; **537**: 31–7.

17 Deussen A, Heusch G, Thämer V. α_2-Adrenoceptor-mediated coronary vasoconstriction persists after exhaustion of coronary vasodilator reserve. *Eur J Pharmacol* 1985; **115**: 147–53.

18 Kallio A, Saraste M, Scheinin M, Hartiala J, Scheinin H. Acute hemodynamic effects of medetomidine and clonidine in healthy volunteers: a noninvasive echocardiographic study. *J Cardiovasc Pharmacol* 1990; **16**: 28–33.

19 Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine–a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; **13**: 635–51.

20 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42.

21 Proctor LT, Schmeling WT, Roerig D, Kampine JP, Warltier DC. Oral dexmedetomidine attenuates hemodynamic responses during emergence from general anesthesia in chronically instrumented dogs. *Anesthesiology* 1991; **74**: 108–14.

22 Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Karki NT. Evidence for medetomidine as a selective and potent agonist at alpha 2-adrenoreceptors. *J Auton Pharmacol* 1986; **6**: 275–84.

23 Salonen JS. Pharmacokinetics of medetomidine. *Acta Vet Scand Suppl* 1989; **85**: 49–54.

24 Docherty JR, McGrath JC. The factors influencing the time course of drug action at α-adrenoceptors: an investigation of the effects of clonidine in the pithed rat. *Br J Pharmac* 1980; **68**: 225–34.

25 Coughlan MG, Lee JG, Bosnjak ZJ, Schmeling WT, Kampine JP, Warltier DC. Direct coronary and cerebral vascular responses to dexmedetomidine. Significance of endogenous nitric oxide synthesis. *Anesthesiology* 1992; **77**: 998–1006.

26 Indolfi C, Piscioni F, Villari B, *et al.* Role of alpha$_2$-adrenoceptors in normal and atherosclerotic human coronary circulation. *Circulation* 1992; **86**: 1116–24.

27 Cavero I, Roach AG. Effects of clonidine on canine cardiac neuroeffector structures controlling heart rate. *Br J Pharmacol* 1980; **70**: 269–76.

28 de Jonge A, Timmermans P, van Zwieten P. Quantitative aspects of alpha adrenergic effects induced by clonidine-like imidazolidines. II. Central and peripheral bradycardic activities. *J Pharmacol Exp Ther* 1982; **222**: 712–9.

29 Kobinger W. Central α-adrenergic systems as targets for hypotensive drugs. *Rev Physiol Biochem Pharmacol* 1978; **81**: 39–100.

30 Hokfelt B, Hederland H, Hansson B. The effect of clonidine and penbutolol, respectively on catecholamine in blood and urine, plasma renin activity and urinary aldosterone in hypertensive patients. *Arch Int Pharmacodyn* 1975; **213**: 307–21.

31 Flacke JW, Flacke WE, Bloor BC, McIntee DF. Hemodynamic effects of dexmedetomidine, an alpha 2-adrenergic agonist, in autonomically denervated dogs. *J Cardiovasc Pharmacol* 1990; **16**: 616–23.

32 Mitrovic V, Hallier E, Kuschke HJ. The haemodynamic effects of clonidine in patients with grade III to IV hypertension. *J Cardiovasc Pharmacol* 1986; **8** (Supp. 3): S51-5.

33 Magorien RD, Hermiller JB, Unverferth DV, Leier CV. Regional hemodynamic effects of clonidine in congestive heart failure. *J Cardiovasc Pharmacol* 1985; **7**: 91–6.

34 Foresti A, Massari FM, Lotto A. Hemodynamic effects of clonidine in patients with acute myocardial infarction complicated by hypertension. *J Cardiovasc Pharmacol* 1986; **8**: S50–2.

35 Zochowski R. Intravenous clonidine in acute myocardial infarction in men. *Int J Cardiol* 1984; **6**: 189–205.

36 Renard M, Liebens I, Waterschoot P, Bernard R. Central inhibition of sympathetic overdrive by clonidine in acute myocardial infarction with systolic hypertension. Haemodynamic study. *Angiology* 1986; **37**: 633–41.

37 Ghignone M, Quintin L, Duke P, Kehler C, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.

38 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

39 Engelman E, Lipszyc M, Gilbart E, *et al.* Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–87.

40 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.

41 Quintin L, Roudot F, Roux C, *et al.* Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *Br J Anaesth* 1991; **66**: 108–15.

42 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992; **75**: 940–6.
43 Aantaa R. Assessment of the sedative effects of dexmedetomidine, an alpha 2-adrenoceptor agonist, with analysis of saccadic eye movements. *Pharmacol Toxicol* 1991; **68**: 394–8.
44 Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Korttila KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991; **73**: 112–8.

CHAPTER 5

The effect of dexmedetomidine on the balance of myocardial energy requirement and oxygen supply and demand†

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The effect of the α_2-adrenergic agonist dexmedetomidine on the balance between myocardial energy requirement and oxygen supply and demand was investigated in 16 open-chest dogs anesthetized with either chloralose/urethane (CU) or fentanyl/halothane (FH). Myocardial energy requirement (estimated from the pressure work index), blood flow and its transmural distribution (radioactive microspheres), as well as myocardial oxygen and lactate extraction were measured before and after administration of dexmedetomidine in doses ranging from 0.1 to 10 μg/kg intravenously. Under CU anesthesia dexmedetomidine decreased heart rate, blood pressure and cardiac output. During FH anesthesia, dexmedetomidine reduced heart rate and cardiac output whereas arterial blood pressure increased. Dexmedetomidine decreased myocardial energy requirement only during CU anesthesia; myocardial oxygen supply and demand decreased in parallel. At the (large) dose of 10 μg/kg, myocardial oxygen extraction increased during both types of anesthesia. Dexmedetomidine ≥1 μg/kg increased endocardial/epicardial blood flow ratio during FH anesthesia. These data indicate that dexmedetomidine ≥1 μg/kg reduces myocardial energy requirements, especially when baseline heart rate and blood pressure are increased. Dexmedetomidine preserves endocardial perfusion and reduces oxygen demand in parallel with oxygen supply and energy requirements.

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Introduction

α_2-Adrenergic agonists are of interest to anesthesiologists because they produce sedation, anxiolysis, analgesia, reduction of anesthetic requirement and hemodynamic stabilization through an action on α_2-adrenergic receptors in the central nervous system [1]. α_2-Adrenergic agonists are being introduced into clinical anesthesia especially for their hemodynamic stabilizing effect [2]. Part of the central action of α_2 agonists can be characterized as sympatholytic [1]. As a consequence, these drugs decrease heart rate and contractility [1,3] leading to a decrease of myocardial energy requirements. Since the heart possesses a powerful autoregulation [4], this decrease in energy requirements could lead to a decrease in coronary blood flow. In this case coronary vascular resistance would increase while the balance between myocardial oxygen supply and oxygen demand is maintained.

A decrease in coronary blood flow could, however, also be due to α-adrenergic vasoconstriction resulting from stimulation of postsynaptic vascular α_2 receptors [5–7]. In this case a reduction in oxygen supply would coincide with increased afterload and increased demand [6,7] and thus cause imbalance between requirements and supply. It is important to understand the interaction of sympatholytic and vasoconstrictive effects of α_2 agonists on the heart since these drugs may be used more often in patients with cardiovascular disease. Therefore we investigated the effect of dexmedetomidine on myocardial oxygen supply, oxygen demand, and energy requirement in two groups of dogs which differed as to type of anesthesia used as well as hemodynamic status. One group, anesthetized with chloralose and urethane (CU), was relatively hyperdynamic compared to the second group, which received fentanyl/halothane anesthesia (FH). In addition, the dog was chosen as the experimental animal because this species is prone to α-adrenergic vasoconstriction [5] so that less desirable effects of dexmedetomidine on the heart, if any, could be elicited more readily.

Methods

These experiments conformed to the Dutch law for animal experimentation, and were approved by the local animal ethical committee. Sixteen adult, healthy, mongrel dogs of either sex weighing between 22 and 39 kg were used for the study. Anasthesia was induced with thiopental (30 mg/kg) and, after endotracheal intubation, the dogs were ventilated with oxygen/nitrous oxide (40%/60%). Subsequently, two different anesthetic regimes were followed. Six animals were anesthetized with 60 mg chloralose and 300 mg urethane intravenously (IV) per kilogram of body weight (CU group). In the other 10 animals, halothane (0.5%–1%) was added to the inspired gases to maintain adequate anesthesia throughout the study. Fentanyl (1–5 μg/kg) was administered IV in the FH group during surgical preparation to keep heart rate (HR) at approximately 100 bpm until baseline measurements were taken.

A venous cannula was inserted in a leg vein for infusion of fluids and medication.

The experimental preparation has been described previously in detail [8]. Catheters were introduced for measurement of aortic and left ventricular pressure (Millar catheter tip). After opening the thorax, a flow probe (Skalar, Delft, The Netherlands) was placed around the left anterior descending coronary artery (LAD). A small polyethelene catheter (PE 60) was inserted into the coronary vein accompanying the LAD in order to obtain regional venous blood samples. The first positive derivative of left ventricular pressure ($LVdP/dt_{max}$) and HR were derived from the left ventricular pressure signal. A thermodilution pulmonary artery catheter introduced via the left external jugular vein was used to obtain mixed venous blood samples from the pulmonary artery and to measure cardiac output by the thermodilution technique. Left ventricular pressure, aortic pressure, coronary flow and electrocardiogram (lead II) were displayed continuously. All pressures and flows were recorded continuously using a pen recorder at 0.25 cm/s, increased to 5 cm/s during data acquisition.

Radioactive microspheres (New England Nuclear, Boston, MA) 15 μm in diameter and labeled with ^{141}Ce, ^{113}Sn, ^{103}Ru, ^{95}Nb, or ^{46}Sc were used to determine regional myocardial blood flow (MBF) by the reference withdrawal method [9] as previously described in detail [8]. Approximately 2.5×10^6 microspheres were injected into the left atrium and a reference sample taken from the brachial artery at a rate of 20.7 mL/min. After killing the dogs with an overdose of pentobarbital, the heart was excised, rinsed, and stored in formaldehyde 5%. Transmural samples were taken from the perfusion area of the LAD (anterior wall) and from the posterior wall and interventricular septum and were divided into subendocardial, mid-wall and subepicardial layers. The myocardial pieces were weighed and counted in a γ counter together with the reference blood samples. From these data MBF ($mL \cdot min^{-1} \cdot g^{-1}$) was calculated with the MIC II program [8].

After completion of instrumentation and a stabilization period of 15 min, baseline measurements were taken and repeated after 10 min. After this, successively increasing doses (0.1, 0.3, 1, 3, and 10 μg/kg) of dexmedetomidine were given IV by slow infusion over 2 min at 20-min intervals and measurements recorded 15 min after administration.

At each sample time the hemodynamic measurements were performed and arterial, mixed venous, and coronary venous blood samples obtained. Radioactive microspheres were injected only at baseline and at doses of 0.1, 1.0, and 10 μg/kg in all animals of the CU group and in eight animals of the FH group.

Endocardial, epicardial, and total coronary vascular resistance (CVR, mm Hg $\cdot$ min $\cdot$ g $\cdot$ mL^{-1}) were calculated as the ratio of the specific MBF ($mL \cdot min^{-1} \cdot g^{-1}$) and mean arterial blood pressure. The endocardial/epicardial blood flow ratio was also calculated. Myocardial oxygen consumption (MVo_2, $\mu mol \cdot min^{-1} \cdot g^{-1}$) was calculated as the product of arterio-local coronary venous difference of oxygen saturation, arterial

hemoglobin concentration (mmol/L) and total MBF (mL · min^{-1} · g^{-1}, being the average of all the samples from the various myocardial layers). Myocardial oxygen supply was calculated as the product of total MBF and arterial oxygen content.

Energy requirement of the left ventricle was estimated from the pressure work index (PWI; arbitrary units, equivalent to μmol · min^{-1} · g^{-1}), as described by Rooke and Feigl [10]:

$$PWI = c1(SBP \times HR) + c2(0.8\ SBP + 0.2\ DBP) \times HR \times SV/BW + c3$$

where

SV = stroke volume (mL)
SBP = systolic blood pressure (mm Hg)
DBP = diastolic blood pressure (mm Hg)
BW = body weight (kg)
$c1$ = 1.63×10^{-4}
$c2$ = 1.30×10^{-4}
$c3$ = 0.57

A two-way analysis of variance for repeated measures was used for intergroup comparisons. Intragroup comparisons were evaluated using one-way analysis of variance for repeated measures. When significance was found, Fisher's protected least significant difference test was used as a *post-hoc* multiple comparison procedure. Baseline values between the two groups were compared using Student's *t*-test. A P value of less than 0.05 was considered significant.

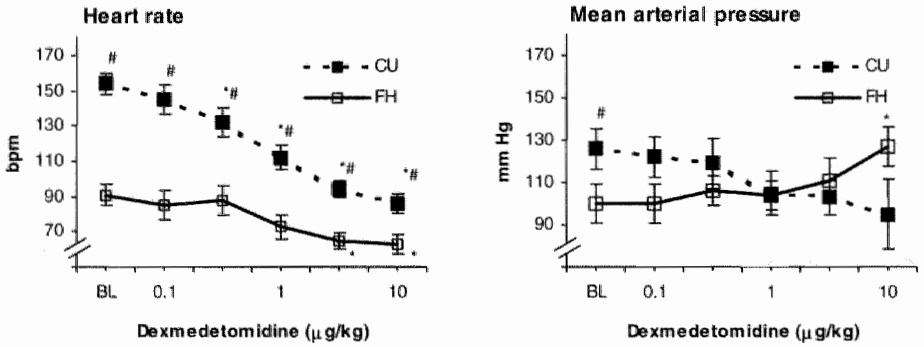

Figure 5-1 Heart rate and mean arterial pressure at baseline (BL) and 15 min after dexmedetomidine 0.1, 0.3, 1, 3, and 10 μg/kg given intravenously over 2 min. Values are mean ± SEM. CU = chloralose/urethane-anesthetized dogs; FH = fentanyl/halothane-anesthetized dogs. * $P < 0.05$ compared to baseline. # $P < 0.05$ FH dogs compared to CU dogs.

Table 5-1 Systemic vascular and cardiac effects of increasing doses of dexmedetomidine

Variable[a]	Group	Dexmedetomidine (μg/kg)					
		Baseline	0.1	0.3	1.0	3.0	10.0
Cardiac output	FH	3.7 ± 0.4	3.6 ± 0.6	3.4 ± 0.4	2.7 ± 0.3*	2.1 ± 0.2*	2.0 ± 0.2*
(L/min)	CU	3.7 ± 0.2	3.5 ± 0.3	3.2 ± 0.3*	2.3 ± 0.2*	1.8 ± 0.3*	1.6 ± 0.2*
SVR (dynes · s	FH	2568 ± 617	2636 ± 517	2900 ± 581	3481 ± 579	4584 ± 701*	5576 ± 692*
· cm^{-5})	CU	2751 ± 256	2898 ± 267	3087 ± 380	3777 ± 402	5227 ± 764*	5016 ± 801*
Stroke volume	FH	40.7 ± 4.6†	42.8 ± 5.5	38.7 ± 4.0	37.6 ± 4.0	32.7 ± 2.9	32.9 ± 4.0
(mL)	CU	25.0 ± 2.4	24.7 ± 2.8	25.1 ± 2.9	21.6 ± 3.1	19.4 ± 2.9*	18.9 ± 2.8*
$LVdP/dt_{max}$	FH	2229 ± 206	2181 ± 179	2169 ± 173	1979 ± 154†	1789 ± 103*†	1852 ± 93*†
(mm Hg/s)	CU	2217 ± 253	1967 ± 187	1617 ± 159*	1350 ± 126*	1267 ± 81*	1117 ± 162*
LVEDP	FH	8.2 ± 1.0	7.4 ± 0.7	7.6 ± 1.1	8.4 ± 1.3	9.9 ± 2.3	11.0 ± 2.8
(mm Hg)	CU	8.3 ± 0.7	8.2 ± 1.4	7.7 ± 1.5	7.0 ± 1.0	9.0 ± 1.4	9.7 ± 2.0
Coronary flow	FH	33.3 ± 5.6	28.4 ± 3.1	26.7 ± 4.1	27.2 ± 3.1	27.6 ± 4.0	23.6 ± 1.7
(mL/min)	CU	35.7 ± 5.0	32.3 ± 3.4	29.7 ± 3.3	22.9 ± 2.8	24.8 ± 3.8	24.7 ± 3.8
CVR (mm Hg	FH	3.8 ± 0.9	3.8 ± 0.5	5.0 ± 1.2	4.7 ± 1.2	4.7 ± 0.7	5.5 ± 0.4
· mL^{-1} · min^{-1})	CU	3.9 ± 0.5	4.0 ± 0.5	4.3 ± 0.7	5.6 ± 1.5	5.6 ± 1.7	5.3 ± 1.6
PWI (μmol	FH	3.98 ± 0.4†	3.91 ± 0.4†	4.42 ± 0.6	3.92 ± 0.5	2.97 ± 0.2	3.30 ± 0.2
· g^{-1} · min^{-1})	CU	6.36 ± 0.6	5.81 ± 0.5	5.44 ± 0.5*	3.82 ± 0.3*	3.12 ± 0.2*	2.73 ± 0.4*
Stroke work	FH	3974 ± 486†	4254 ± 551	4059 ± 404	3866 ± 374	3572 ± 384	4123 ± 505
(mL · mm Hg)	CU	3134 ± 361	3080 ± 477	3031 ± 485	2371 ± 460*	2017 ± 366*	1945 ± 545*

Values are expressed as mean ± SEM. FH = dogs anesthetized with fentanyl and halothane; CU = dogs anesthetized with chloralose/urethane; SVR = systemic vascular resistance; $LVdP/dt_{max}$ = first positive derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; CVR = coronary vascular resistance; PWI = pressure work index. [a] For each variable, the measurements are: baseline and effect 15 min after dexmedetomidine in the doses shown. * $P < 0.05$ compared to baseline. † $P < 0.05$ FH compared to CU dogs.

Results

Hemodynamics

Baseline hemodynamics of the two groups differed significantly (Table 5-1). HR and mean arterial pressure (MAP) values were higher in the CU than in the FH dogs (Figure 5-1). Differences in $LVdP/dt_{max}$ and left ventricular end-diastolic pressure were not statistically significant. SV and stroke work were significantly greater in the FH group, but PWI was significantly higher in the CU group. In both groups dexmedetomidine administration caused a dose-dependent decrease of HR, significant at doses ≥ 0.3 and 1 μg/kg in CU and FH dogs, respectively. MAP increased in the FH group but tended to decrease in the CU group. The decrease in CO and increase in systemic vascular resistance was similar in both groups. SV decreased significantly in the CU but not in the FH group. $LVdP/dt_{max}$ decreased significantly at doses ≥ 0.3 and 3 μg/kg in the CU and FH groups, respectively (Table 5-1). PWI, an index of myocardial energy requirement, decreased. In the CU group this decrease became significant at 0.3 μg/kg and was as large as 57% at 10 μg/kg. No significant change was seen in the FH group (Table 5-1).

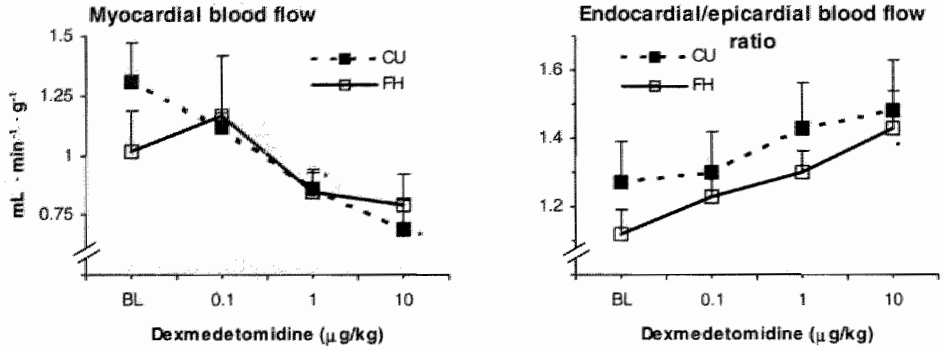

Figure 5-2 Effect of dexmedetomidine on total transmural myocardial blood flow and endocardial/epicardial blood flow ratio. Measurements at baseline (BL) and 15 min after 2 min intravenous infusion of dexmedetomidine 0.1, 1, and 10 μg/kg. Values are mean ± SEM. CU = chloralose/urethane-anesthetized dogs; FH = fentanyl/halothane-anesthetized dogs. * $P < 0.05$ compared to baseline.

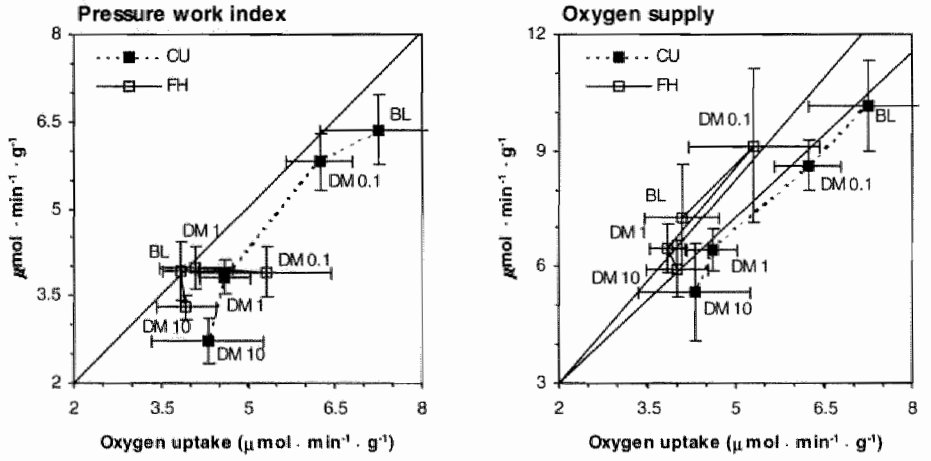

Figure 5-3 Relationship between oxygen uptake and pressure work index (left panel) and oxygen supply (right panel). Values are mean ± SEM. CU = chloralose/urethane-anesthetized dogs. FH = fentanyl/halothane-anesthetized dogs. Baseline (BL) and 15 min after slow (2 min) intravenous infusion of dexmedetomidine (DM) 0.1, 1, and 10 μg/kg. The lines represent the line of unity (left panel) and line of 57% (right panel, upper) and 69% oxygen extraction (right panel, lower). Data in the left panel indicate that pressure work index (estimate of myocardial energy requirement) changes proportional to oxygen uptake. The right panel demostrates that at DM ≤ 1 μg/kg changes in oxygen uptake and supply are proportional, indicating metabolic regulation of myocardial blood flow.

Table 5-2 Effect of increasing doses of dexmedetomidine on myocardial blood flow, coronary vascular resistance and MVo_2

Variable[a]	Group	Dexmedetomidine (μg/kg)			
		Baseline	0.1	1.0	10.0
Blood flow ($mL \cdot min^{-1} \cdot g^{-1}$)					
Epicardial	FH	0.97 ± 0.16	1.05 ± 0.21	0.73 ± 0.08	0.65 ± 0.09*
	CU	1.16 ± 0.15	0.97 ± 0.05	0.70 ± 0.06*	0.55 ± 0.09*
Endocardial	FH	1.10 ± 0.20	1.32 ± 0.28	0.93 ± 0.11	0.93 ± 0.17
	CU	1.44 ± 0.18	1.26 ± 0.12	0.99 ± 0.09*	0.79 ± 0.15*
Vascular resistance ($mm\ Hg \cdot min \cdot g \cdot mL^{-1}$)					
Epicardial	FH	121.8 ± 29.6	109.5 ± 22.0	166.5 ± 24.5	227.3 ± 32.1*
	CU	117.4 ± 17.3	128.6 ± 12.9	179.2 ± 32.0	208.9 ± 37.4*
Endocardial	FH	110.9 ± 25.0	90.3 ± 17.6	128.4 ± 16.2	163.6 ± 22.2*
	CU	91.8 ± 12.1	99.4 ± 6.2	122.4 ± 18.0	136.0 ± 17.8
Total MVo_2	FH	4.10 ± 0.63†	5.31 ± 1.12	3.84 ± 0.31	3.93 ± 0.52
($\mu mol \cdot min^{-1} \cdot g^{-1}$)	CU	7.26 ± 0.60	6.23 ± 0.58	4.60 ± 0.43*	4.31 ± 0.96*

Values are expressed as mean ± SEM. FH = dogs anesthetized with fentanyl and halothane; CU = dogs anesthetized with chloralose/urethane; MVo_2 = myocardial oxygen consumption. [a] For each variable, the measurements are: baseline and effect 15 min after dexmedetomidine in the doses shown. * $P < 0.05$ compared to baseline. † $P < 0.05$ FH dogs compared with CU dogs.

Myocardial blood flow and vascular resistance

The effect of dexmedetomidine on MBF was different between the two experimental groups as well as between the various layers of the left ventricular wall (Table 5-2). At doses ≥ 1 μg/kg total transmural (Figure 5-2) as well as epi- and endocardial blood flow decreased dose dependently in the CU group. In the FH group the only significant change was in the epicardial blood flow after 10 μg/kg (Table 5-2). However, dexmedetomidine altered the distribution of blood flow between the various layers of the ventricular wall, especially in the FH group as evidenced by a significant increase in the endocardial/epicardial blood flow ratio (Figure 5-2). Dexmedetomidine 10 μg/kg significantly increased epi- and endocardial CVR compared to baseline.

Myocardial lactate and oxygen uptake

At all sample times in all experiments the aortocoronary lactate difference was positive and dexmedetomidine did not influence this variable (Table 5-3).

At baseline aortocoronary oxygen saturation difference was approximately 0.12 higher in the CU than in the FH group ($P < 0.05$). In both groups aortocoronary oxygen saturation difference tended to increase with increasing doses of dexmedetomidine, but this increase (by approximately 0.10) was only significant at the highest dose in both groups (Table 5-3).

Table 5-3 Effect of increasing doses of dexmedetomidine on oxygen saturation and lactate extraction

Variable[a]	Group	Dexmedetomidine (μg/kg)					
		Baseline	0.1	0.3	1.0	3.0	10.0
O_2sat(A–V) (%)	FH	0.31 ± 0.03	0.32 ± 0.04	0.29 ± 0.02†	0.32 ± 0.03†	0.41 ± 0.04*†	0.43 ± 0.04*†
	CU	0.33 ± 0.03	0.34 ± 0.03	0.37 ± 0.05	0.45 ± 0.04	0.60 ± 0.08*	0.61 ± 0.04*
O_2sat(A–C) (%)	FH	0.57 ± 0.05†	0.59 ± 0.03	0.61 ± 0.02	0.61 ± 0.03	0.64 ± 0.02	0.67 ± 0.03*
	CU	0.69 ± 0.04	0.70 ± 0.03	0.68 ± 0.04	0.70 ± 0.02	0.74 ± 0.03	0.80 ± 0.02*
Lactate (A–C) (mmol/L)	FH	0.82 ± 0.27	0.72 ± 0.23	0.46 ± 0.36	0.73 ± 0.25	0.45 ± 0.30	0.91 ± 0.40
	CU	0.61 ± 0.30	0.57 ± 0.23	0.54 ± 0.22	0.62 ± 0.23	0.60 ± 0.22	0.62 ± 0.17

Values are expressed as mean ± SEM. FH = dogs anesthetized with fentanyl and halothane; CU = dogs anesthetized with chloralose/urethane; O_2sat(A–V) = arterio-mixed venous saturation difference; O_2sat(A–C) = arteriocoronary venous saturation difference; Lactate (A–C) = arteriocoronary venous lactate difference. [a] For each variable, the measurements are: baseline and effect 15 min after dexmedetomidine in the doses shown. * $P < 0.05$ compared to baseline. † $P < 0.05$ FH dogs compared to CU dogs.

The decrease of MVo_2 in the CU group (approximately 40%, $P < 0.05$ at 1 and 10 μg/kg dexmedetomidine) was less pronounced than the decrease in total MBF (approximately 48%). In the FH group MVo_2, like MBF, remained essentially unchanged (Table 5-2).

Relation between myocardial energy requirement and oxygen supply and demand

To illustrate the relation of the changes in MVo_2 to those of myocardial energy requirements, PWI was plotted as a function of MVo_2 (Figure 5-3, left panel). In the CU group, dexmedetomidine shifted the PWI-MVo_2 relation parallel to the line of identity (diagonal line). Only at a dose of 10 μg/kg dexmedetomidine was a deflection away from the identity line observed, indicating that MVo_2 decreased less than PWI. To analyze the influence of dexmedetomidine on the regulation of myocardial blood flow we plotted myocardial arterial oxygen supply as a function of myocardial oxygen demand, as introduced by Mohrman and Feigl [11] (Figure 5-3, right panel). In the CU group dexmedetomidine up to a dose of 1 μg/kg caused a shift from upper right to lower left, parallel to a line representing 69% extraction. At the highest dose (10 μg/kg) the supply-demand relation shifted more downwards, due to the increased oxygen extraction. The supply-demand relationship of the FH group was shifted upwards and leftwards compared to that of the CU group, due to the lower oxygen extraction. In the FH group, the supply-demand relationship also shifted downwards at a dose of 10 μg/kg of dexmedetomidine.

Discussion

The results from the present study demonstrate that the hemodynamic effects of dexmedetomidine may be influenced by the type of anesthesia as has been demonstrated for the cerebrovascular circulation [12]. Dexmedetomidine decreases myocardial energy requirement and MVo_2, especially when baseline HR and MAP are

high, as seen in the CU group. Most of the changes in MBF and oxygen supply after dexmedetomidine are due to changes in energy requirement. The increased myocardial oxygen extraction at 10 μg/kg suggests some α-adrenergic vasoconstriction at this high dose. Dexmedetomidine also increases the endocardial/epicardial blood flow ratio. This seems to be the result of predominant epicardial vasoconstriction, bradycardia, and (for the FH group) increase in blood pressure.

Chloralose and urethane (ethyl carbamate) are used as anesthetics for acute animal experiments, especially because they have few effects on cardiac function [13] and cardiovascular reflexes [14]. It has been suggested that urethane may activate the sympathetic outflow from the central nervous system [15]. Halothane depresses baroreflex activity [16] and reduces contractility [17], HR, blood pressure, and MVo_2 [18]. Fentanyl increases vagal tone [19] and reduces sympathetic tone [20]. Therefore, it is likely that baseline sympathetic tone was higher in the CU dogs and parasympathetic tone higher in the FH dogs. This is supported by the higher baseline HR and MAP, and consequently PWI, in the CU group. It was in this group that the hemodynamic response to dexmedetomidine was most similar to that reported in concious dogs [21] and in humans [22].

During both types of anesthesia, dexmedetomidine caused a similar decrease of HR and increase of systemic vascular resistance and CVR. However, the reduction in contractility was greater in the CU than in the FH dogs (as indicated by the larger decreases in cardiac output, stroke work and $LVdP/dt_{max}$). Moreover, MAP decreased during CU anesthesia while it increased during FH anesthesia. These data suggest that the vasoconstrictive effect is directly related to stimulation of peripheral vascular α_2 receptors, whereas changes in contractility and blood pressure are dependent on the state of activity of the autonomic nervous system.

A primary question in the present study was how dexmedetomidine interferes with the balance between myocardial oxygen supply and demand. It was observed that at doses up to 1 μg/kg dexmedetomidine's sympatholytic effects exceeded its vasoconstrictive effects. At these doses dexmedetomidine caused an equivalent decrease in PWI and oxygen uptake during CU anesthesia, whereas dexmedetomidine did not change these variables in the FH group. Thus changes in MVo_2 were related to changes in energy requirements. Moreover, changes in MVo_2 occurred almost exclusively due to changes in MBF, as indicated by the absence of significant changes in myocardial oxygen extraction. This is a behaviour similar to that observed when HR is varied by atrial pacing [23] but different from the effect of a noradrenaline infusion or bicarotid artery occlusion [11]. Both these interventions increase MBF as well as oxygen extraction [11]. Representing their results as a graph of oxygen supply versus oxygen demand (similar to Figure 5-3), Mohrman and Feigl [11] concluded that α-adrenergic stimulation impaired 30% of the increase of MBF. In our study the unaltered oxygen extraction at doses up to 3 μg/kg indicates that dexmedetomidine does not significantly limit MBF by adrenergic vasoconstriction at this dosage. The increase of myocardial oxygen extraction at a dose of 10 μg/kg in both groups indicates that,

under these conditions, dexmedetomidine limits MBF through α-adrenergic vasoconstriction by about 10%–15%. Because dexmedetomidine has complex hemodynamic effects, changes in myocardial energy requirements could not be estimated from a single variable. We used the PWI for this purpose because it accurately predicts changes in MVo_2 due to changes in afterload and adrenergic stimulation [10,24].

The finding in the CU group that MVo_2 decreased in proportion to PWI, in combination with the unaltered lactate arteriovenous difference, indicates that the balance between myocardial energy requirement and MVo_2 is maintained at increasing doses of dexmedetomidine. Halothane decreases MVo_2 [18] as reflected in the lower baseline value of the FH group. The increased MAP after dexmedetomidine should increase in MVo_2 but, because of the reduction in HR, the product of MAP and HR remains constant and is correlated to MVo_2 in halothane-anesthetized dogs [18].

The results from the microsphere measurements demonstrate that α_2 stimulation by dexmedetomidine increases endocardial/epicardial blood flow ratio, especially in the FH group. These results seem in agreement with the finding that α-adrenergic blockade decreases endocardial/epicardial blood flow ratios in normally perfused as well as underperfused myocardium [25]. Both results indicate that predominantly epicardial vasoconstriction occurs by an α-adrenergic mechanism.

Since there is no evidence for a transmural gradient in the density of coronary α-adrenergic receptors or of sympathetic nerves [26], these findings are possibly explained by a stronger metabolic vasodilatory regulation in the endocardium as compared to the epicardium [4], so that adrenergic vasoconstriction can be obtunded in the endocardium but not in the epicardium. This possibility is supported by evidence that hypoxia and acidosis can impair adrenergic coronary vasoconstriction [27,28]. In the present study, the changes in endocardial/epicardial blood flow ratio may also be due, in part, to the hemodynamic effects of dexmedetomidine. A decrease in HR, observed in both groups, is known to be beneficial for blood flow to the endocardial layers. Such a redistribution has been observed during variation of heart rate with atrial pacing [23,29] as well as after administration of β-blockers [30,31].

These data seem in conflict with the opinion that α_2-receptor stimulation plays an important role in the origination of myocardial ischemia [5]. However, that concept was derived primarily from experiments with maximal sympathetic stimulation and α-adrenergic blockade, conditions quite different from that in the present study.

The present results demonstrate that myocardial energy requirement decreases at 1 μg/kg dexmedetomidine, whereas moderate coronary vasoconstriction (as shown by the increased oxygen extraction) occurs after 10 μg/kg. Because the dose currently used for premedication in anesthesia is between 0.5 and 2 μg/kg [32], the myocardial energy sparing effect of dexmedetomidine most likely prevails. This comparison between human and canine dexmedetomidine doses seems justified, since a 2-min IV

infusion of 1 μg/kg in dogs gave a plasma level after 15 min of 0.61 ± 0.19 ng/mL (mean ± SD) [33]. The same infusion in humans resulted in plasma levels of 0.94 ± 0.18 after 10 min and 0.29 ± 0.04 ng/mL after 60 min [22].

Indolfi *et al.* [34] showed that the human CVR may increase by a maximum of 28% after intracoronary administration of an α_2-adrenergic agonist, a value less than half the maximum observed in the present study. Therefore, at comparable doses, coronary α_2-adrenergic vasoconstriction may be the less pronounced in humans than in dogs. Since the sympathetic tone is generally higher in conscious humans than in anesthetized dogs, the myocardial energy-saving effect most likely prevails in clinical use.

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References

1 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605.
2 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–19.
3 Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2-adrenergic agonist, in halothane-anesthetized dogs. *Anesth Analg* 1988; **67**: 611–15.
4 Feigl EO. Coronary physiology. *Physiol Rev* 1983; **63**: 1–205.
5 Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation* 1990; **81**: 1–13.
6 Bloor BC, Frankland M, Alper G, *et al.* Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992; **263(2)**: 690–7.
7 Flacke WE, Flacke JW, Bloor BC, *et al.* Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7(1)**: 41–9.
8 Prinzen FW, Van der Vusse GJ, Reneman RS. Blood flow distribution in the left ventricular free wall in open-chest dogs. *Basic Res Cardiol* 1981; **76**: 431–7.
9 Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labeled microspheres. *Prog Cardiovasc Dis* 1977; **20**: 55–79.
10 Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. *Circ Res* 1982; **50**: 273–86.
11 Mohrman DE, Feigl EO. Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. *Circ Res* 1978; **42**: 79–86.
12 Fale A, Kirsch JR, McPherson RW. Alpha 2-adrenergic agonist effects on normocapnic and hypercapnic cerebral blood flow in the dog are anesthetic dependent. *Anesth Analg* 1994; **79(5)**: 892–8.

13 Lang RM, Marcus RH, Neumann A, *et al.* A time-course study of the effects of pentobarbital, fentanyl, and morphine chloralose on myocardial mechanics. *J Appl Physiol* 1992; **73(1)**: 143–50.
14 Maggi CA, Meli A. Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 2: Cardiovascular system. *Experientia* 1986; **42(3)**: 292–7.
15 Maggi CA, Meli A. Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 1: General considerations. *Experientia* 1986; **42(2)**: 109–14.
16 Seagard JL, Hopp FA, Donegan JH, *et al.* Halothane and the carotid sinus reflex: evidence for multiple sites of action. *Anesthesiology* 1982; **57**: 191–202.
17 Trigt vP, Christian CC, Fagraeus L, *et al.* Myocardial depression by anesthetic agents (halothane, enflurane and nitrous oxide): quantitation based on end-systolic pressure-dimension relations. *Am J Cardiol* 1984; **53(1)**: 243–7.
18 Wilkinson PL, Tyberg JV, Moyers JR, White AE. Correlates of myocardial oxygen consumption when afterload changes during halothane anesthesia in dogs. *Anesth Analg* 1980; **59**: 233–9.
19 Inoue K, Samodelor LF, Arndt JO. Fentanyl activates a particular population of vagal efferentes which are cardioinhibitory. *Naunyn-Schmiedebergs Arch Pharmacol* 1980; **312(1)**: 57–61.
20 Laubie M, Schmitt H, Drouillat M. Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic agent fentanyl. *Naunyn-Schmiedebergs Arch Pharmacol* 1977; **296**: 255–61.
21 Schmeling WT, Kampine JP, Roerig DL, Warltier DC. The effects of the stereoisomers of the alpha 2-adrenergic agonist medetomidine on systemic and coronary hemodynamics in conscious dogs. *Anesthesiology* 1991; **75(3)**: 499–511.
22 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77(6)**: 1134–42.
23 Weiss HR. Regional oxygen consumption and supply in the heart: effect of atrial pacing. *Am J Physiol* 1979; **236**: H231–7.
24 Schipke JD, Burkhoff D, Kass DA, *et al.* Hemodynamic dependence of myocardial oxygen consumption indexes. *Am J Physiol* 1990; **258**: H1281–91.
25 Nathan HJ, Feigl EO. Adrenergic vasoconstriction lessens transmural steal during coronary hypoperfusion. *Am J Physiol* 1986; **250**: H645–53.
26 Chilian WM, Harrison DG, Haws CW, *et al.* Adrenergic coronary tone during submaximal exercise in the dog is produced by circulating catecholamines. Evidence for adrenergic denervation supersensitivity in the myocardium but not in coronary vessels. *Circ Res* 1986; **58(1)**: 68–82.
27 Heistad DD, Abboud FM, Mark AL, Schmid. Effect of hypoxemia on responses to noradrenaline and angiotensin in coronary and muscular vessels. *J Pharmacol Exp Ther* 1975; **193**: 941–50.
28 Curro FA, Greenberg S. Characteristics of postsynaptic alpha1 and alpha2 adrenergic receptors in canine vascular smooth muscle. *Can J Physiol Pharmacol* 1983; **61**: 893–904.
29 Becker L. Effect of tachycardia on left ventricular blood flow distribution during coronary occlusion. *Am J Physiol* 1976; **230**: 1072–7.
30 Becker LC, Fortuin NJ, Pitt B. Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ Res* 1970; **28**: 263–9.
31 Gross GJ, Winbury MM. Beta adrenergic blockade on intramyocardial distribution of coronary blood flow. *J Pharmacol* 1973; **187**: 451–64.
32 Aantaa R, Scheinin M. Alpha$_2$-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand* 1993; **37**: 433–48.
33 Roekaerts PM, Prinzen FW, Lange Sd. Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1996; **10**: 619–26.
34 Indolfi C, Piscioni F, Villari B, *et al.* Role of alpha$_2$-adrenoceptors in normal and atherosclerotic human coronary circulation. *Circulation* 1992; **86**: 1116–24.

CHAPTER 6

The effect of dexmedetomidine on nutrient organ blood flow†

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The α_2-adrenergic agonist dexmedetomidine decreases not only heart rate, myocardial contractility, and oxygen demand, but also cardiac output (CO). To investigate whether this reduction in CO could critically impair perfusion of individual organs, we studied the effect of dexmedetomidine on nutrient blood flow to heart, brain, kidney, spleen, skin, intestine, liver, and arteriovenous anastomoses using the radioactive microsphere technique. Studies were conducted in 14 dogs with an open chest and anesthetized with either chloralose/urethane (CU) or fentanyl/halothane (FH), to create different baseline conditions. Hemodynamic variables, organ blood flow, arterial and mixed venous oxygen, and lactate content were measured before and after administration of 0.1, 1, and 10 μg/kg dexmedetomidine intravenously (IV). After 10 μg/kg dexmedetomidine CO decreased in both groups by 50%. The decrease in blood flow varied greatly between the organs. While flow through arteriovenous anastomoses and skin decreased by 70% to 90%, renal blood flow decreased by 30%, cerebral blood flow only when baseline blood flow was high (FH dogs), and left ventricular blood flow only in the CU group, where the largest decrease in hemodynamic variables occurred. Oxygen consumption decreased only in CU dogs, but so did arterial lactate levels. These data indicate that dexmedetomidine causes considerable redistribution of CO, predominantly reducing blood flow to less vital organs and shunt flow.

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Introduction

α_2-Adrenergic agonists, like clonidine, mivazerol, and dexmedetomidine, alter systemic hemodynamics by stimulation of central α_2-adrenoceptors, thereby decreasing sympathetic outflow, heart rate, and myocardial contractility [1]. Previous studies from our laboratory showed that acute administration of dexmedetomidine and mivazerol reduces oxygen requirements of the ventricle due to the reductions in heart rate and contractility [2,3]. In combination with the redistribution of blood flow from epicardial to endocardial layers of the ventricular wall [2], this reduced workload of the heart had favorable effects during myocardial ischemia [3,4]. However, these beneficial effects for the heart were accompanied by decreases in cardiac output (CO) of up to 50% in anesthetized [2,5] and conscious dogs [6], while in humans a decrease of 41% has been reported [7].

No study has indicated whether a reduction in CO by dexmedetomidine critically impairs perfusion and oxygen supply of vital organs. Because the number of α_2-receptors varies considerably from organ to organ, some organs might be affected more than others.

To investigate this question, dexmedetomidine was administered to anesthetized dogs and blood flow in various organs was measured by the radioactive microsphere technique [8]. Systemic oxygen consumption and plasma lactate concentration were also measured. To evaluate the effect of differences in baseline condition on the various actions of dexmedetomidine, two groups of dogs were compared. One group was anesthetized with chloralose and urethane (CU group), the other with fentanyl and halothane (FH group). These two anesthetic techniques are known to affect the autonomic system in different ways [2].

Methods

All animal experiments were performed after approval of the animal experimental committee of the University of Limburg, Maastricht, The Netherlands. Fourteen healthy, mongrel dogs of either sex weighing 22–39 kg were studied. Anesthesia was induced with the short-acting barbiturate thiopental (30 mg/kg) and, after endotracheal intubation, the dogs were ventilated with oxygen/nitrous oxide (40%/60%). Subsequently two different anesthetic regimes were followed. Six animals were anesthetized with 60 mg chloralose and 300 mg urethane intravenously (IV) per kilogram of body weight (CU group). In the other eight animals halothane (0.5%–1%) was added to the inspired gases to maintain adequate anesthesia throughout the study. Fentanyl (1–5 μg/kg) was administered IV in the FH group during surgical preparation. A venous cannula was inserted in a leg vein for infusion of fluids and medication.

The experimental preparation has been described previously in detail [2,9]. Catheters were introduced in brachial and femoral arteries for measurement of aortic and left

ventricular (LV) pressure. A thermodilution pulmonary artery catheter introduced via the left external jugular vein was used to obtain mixed venous blood samples from the pulmonary artery and to measure CO by the thermodilution technique. LV pressure, aortic pressure, coronary flow, and electrocardiogram (lead II) were displayed continuously. All pressures and flows were recorded continuously using a pen recorder at 0.25 cm/s, increased to 5 cm/s during data acquisition.

Radioactive microspheres (New England Nuclear, Boston, MA) 15 μm in diameter and labeled with ^{141}Ce, ^{113}Sn, ^{103}Ru, ^{95}Nb, or ^{46}Sc were used to determine nutrient organ blood flow. Approximately 2.5×10^6 microspheres were injected into the left atrium and an arterial reference sample was taken from the brachial artery at a rate of 20.7 mL/min. At each dose of dexmedetomidine one of the isotopes was injected. Since the 15-μm spheres are distributed through the body relative to the volume flow to each organ and lodge in the microcirculation, the number of microspheres measured after the experiments represents the flow to that organ at the time of injection. After the dogs were killed with an overdose of pentobarbital, their organs were excised, rinsed, and stored in formaldehyde 5%. For blood flow determination multiple, representative samples of 1–3 g were taken randomly from each organ (cerebral cortex samples, containing mainly gray matter, left ventricle, both lungs, thoracic skin, kidneys, spleen, intestine, and liver). Use of this calculation for the lung samples yields a measure of the absolute amount of shunt flow, since all microspheres passing through arteriovenous shunts larger than 15 μm lodge in the lungs. The pieces were weighed to the nearest milligram and counted in a γ counter (Packard Multichannel Analyzer, Brussels, Belgium or LKB Compugamma 1282, Turku, Finland), together with the reference blood samples. Using the gammaspectra the contribution from each of the injected isotopes could be determined and nutrient organ blood flow in mL · min^{-1} · 100 g^{-1} calculated with the MIC II program [9]. Absolute blood flow values were calculated using the equation [8]:

$$BF_{tissue} = I_{tissue} \times Q_{art.ref.} / I_{art.ref.} \times W_{tissue}$$

where BF_{tissue} is blood flow to the tissue (mL · min^{-1} · 100 g^{-1}), I_{tissue} and $I_{art.ref.}$ are the radioactivity of the tissue and arterial reference sample, respectively, and W_{tissue} is the weight of the tissue.

Fifteen minutes after completion of instrumentation, baseline measurements were taken and repeated after 10 min. After the baseline measurements, successively increasing doses (0.1, 1, and 10 μg/kg) of dexmedetomidine were given IV by slow infusion over 2 min at 40-min intervals. Fifteen minutes after each administration, the hemodynamic measurements were performed, arterial and mixed venous samples obtained, and radioactive microspheres injected.

Arterial and mixed venous blood gases, blood pH, hemoglobin (Hb) concentration, and oxygen saturation were determined. Oxygen content was calculated from the latter variables.

Table 6-1 Hemodynamic effects of dexmedetomidine

Variable	Group	Dexmedetomidine (μg/kg)			
		Baseline	0.1	1.0	10.0
Cardiac output (L/min)	CU	3.7 ± 0.2	3.5 ± 0.3	2.3 ± 0.2*	1.6 ± 0.2*
	FH	3.7 ± 0.4	3.6 ± 0.6	2.7 ± 0.3	2.0 ± 0.2*
Mean arterial blood pressure (mm Hg)	CU	126 ± 9.5†	123 ± 9.7	105 ± 10.2	95 ± 16.8
	FH	100 ± 9.6	100 ± 8.9	104 ± 7.0	127 ± 9.0*
Heart rate (bpm)	CU	154 ± 8.4†	145 ± 7.7†	112 ± 9.7*†	86 ± 8.4*†
	FH	91 ± 5.9	85 ± 8.7	73 ± 6.9	63 ± 5.7*
SVR (dynes · s · cm^{-5})	CU	2751 ± 256	2898 ± 267	3777 ± 402	5016 ± 801*
	FH	2568 ± 617	2636 ± 517	3481 ± 579	5576 ± 692*
Stroke volume (mL)	CU	25.0 ± 2.4†	24.7 ± 2.8	21.6 ± 3.1	18.9 ± 2.8*
	FH	40.7 ± 4.6	42.8 ± 5.5	37.6 ± 4.0	32.9 ± 4.0

Values are expressed as mean ± SEM. CU = dogs anesthetised with chloralose/urethane; FH = dogs anesthetised with fentanyl/halothane; SVR = systemic vascular resistance. * Significantly different from baseline ($P < 0.05$). † Significant difference between CU and FH at this dose.

Systemic vascular resistance (SVR) was calculated as mean arterial pressure (MAP) × 80 / CO (dynes · s · cm^{-5}). Mixed venous oxygen extraction (mL/dL blood) was calculated as: Hb × 1.34 × (Sao_2 – Svo_2) where Hb is in grams per deciliter, Sao_2 is arterial oxygen saturation, and Svo_2 is mixed venous oxygen saturation (the small contribution of dissolved oxygen was not taken into account). Total body oxygen uptake was calculated as the product of oxygen extraction and CO. Two-way analysis of variance

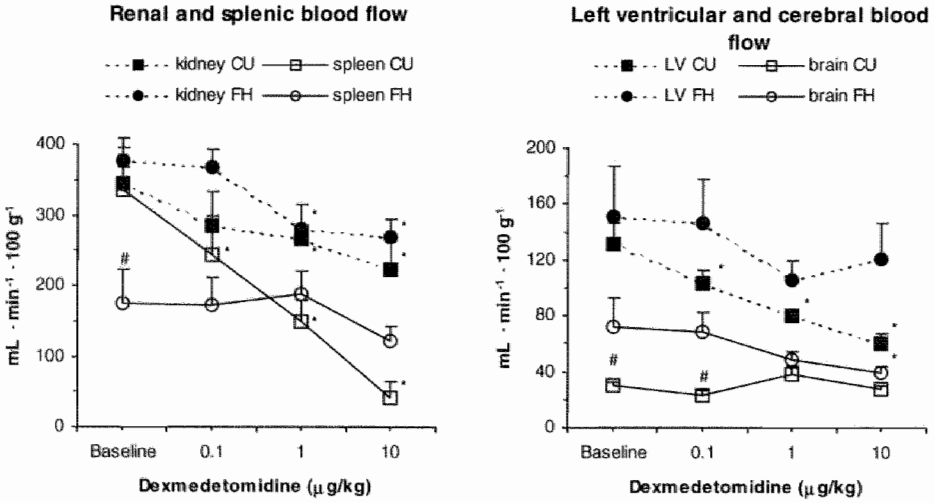

Figure 6-1 Effect of dexmedetomidine on organ blood flow in dogs anesthetized with either chloralose/urethane (CU) or fentanyl/halothane (FH). Values are expressed as mean ± SEM. LV = left ventricular blood flow. * Significantly different from baseline. # Significant difference between the two groups.

for repeated measures was first applied to detect statistical differences between groups. If the two-way analysis also indicated significant changes within groups, this was further evaluated using one-way analysis of variance for repeated measures and Fisher's protected least significant difference test as a *post-hoc* multiple comparison procedure. Baseline values between the two groups were compared using Student's *t*-test. P values < 0.05 were considered significant.

Results

Baseline hemodynamics of the two groups were different (Table 6-1). Mean heart rate and MAP values were 91 bpm and 100 mm Hg in the FH group and 154 bpm and 126 mm Hg in the CU group. Stroke volume was significantly larger in the FH group (Table 6-1).

In both groups, dexmedetomidine administration caused a dose-dependent decrease in heart rate. Whereas MAP increased significantly in the FH group (from 100 to 127 mm Hg after the 10-μg/kg dose), it tended to decrease in the CU group (from 126 to 95 mm Hg). CO decreased and systemic vascular resistance increased significantly in both groups. Baseline CO, as well as blood flow in most organs, did not differ between the two groups. However, baseline cerebral blood flow (CBF) was significantly higher in the FH group and splenic and muscular blood flow were higher in the CU group (Figures 6-1 and 6-2).

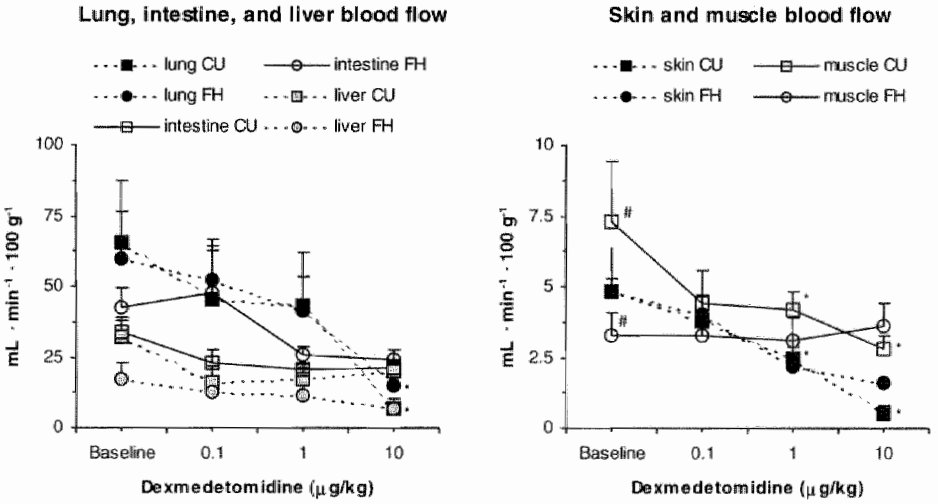

Figure 6-2 Effect of dexmedetomidine on organ blood flow in dogs anesthetized with either chloralose/urethane (CU) or fentanyl/halothane (FH). Values are expressed as mean ± SEM. Lung CU and lung FH were significantly lower than baseline after 10 μg/kg. * Significantly different from baseline. # Significant difference between the two groups.

CBF decreased in one of six dogs in the CU group, but in five of eight experiments in the FH group. CBF mainly decreased in the experiments where baseline values were high, and in these cases dexmedetomidine decreased CBF to values similar to the baseline values of most of the experiments (Figure 6-1). The change in CBF was only significant in the FH dogs after 10 μg/kg. The changes in LV blood flow were different between the two experimental groups. Total LV blood flow decreased dose-dependently in the CU group. In contrast, no significant change of LV flow was found in the FH group (Figure 6-1).

There was also a marked difference in the effect of dexmedetomidine on the splenic flow between the two groups. Initially, flow was higher in the CU group (Figure 6-1) but this decreased significantly after 0.1, 1, and 10 μg/kg, while the flow in the FH group did not change after dexmedetomidine. Dexmedetomidine 1 μg/kg decreased blood flow to the kidneys by 25% and in the skin by 50% in both groups, and the 10-μg/kg dose caused slightly larger decreases (Figure 6-1). Blood flow through arterio-venous anastomoses ("lung flow") decreased by 90% (CU) and 75% (FH) after 10 μg/kg. Blood flow to the skeletal muscle was low and a further reduction was only observed in the CU group. Changes in blood flow in intestine and liver were not significant (Figure 6-2).

Dexmedetomidine increased mixed venous oxygen extraction dose-dependently, the increase becoming significant at a dose of 1 μg/kg in the CU dogs and 10 μg/kg in FH dogs (Table 6-2). Total body oxygen uptake was reduced in the CU dogs after 1 and 10 μg/kg. Arterial lactate concentration was significantly reduced after 1 and 10 μg/kg in the CU group and did not change significantly in the FH group (Table 6-2).

Table 6-2 Effect of increasing doses of dexmedetomidine on oxygen consumption and lactate concentration

Variable	Group	Dexmedetomidine (μg/kg)			
		Baseline	0.1	1.0	10.0
S_{VO_2} (%)	CU	67.3 ± 3.3	65.8 ± 3.3	55.1 ± 4.4*	39.4 ± 4.8*
	FH	65.4 ± 2.1	62.7 ± 3.7	64.6 ± 3.8	53.8 ± 4.4
$C(a\text{-}v)O_2$	CU	5.05 ± 0.25	5.21 ± 0.26	6.84 ± 0.41*	9.28 ± 0.20*
(mL O_2/dL blood)	FH	4.54 ± 0.77	5.35 ± 0.41	5.40 ± 0.50	7.22 ± 0.56*
VO_2 (mL/min)	CU	197 ± 18.9	187 ± 16.1	160 ± 14.3*	150 ± 24.0*
	FH	142 ± 15.3	173 ± 35.0	141 ± 20.4	131 ± 14.2
Arterial lactate	CU	2.07 ± 0.49	1.88 ± 0.48	1.73 ± 0.46*	1.48 ± 0.41*
(mmol/L)	FH	1.21 ± 0.41	1.13 ± 0.32	1.15 ± 0.35	1.04 ± 0.24

Values are expressed as mean ± SEM. CU = dogs anesthetised with chloralose/urethane; FH = dogs anesthetised with fentanyl/halothane; S_{VO_2} = mixed venous oxygen saturation; $C(a\text{-}v)O_2$ = mixed venous oxygen extraction; V_{O_2} = total body oxygen consumption. * Significantly different from baseline ($P < 0.05$). There were no significant differences between the two groups.

Discussion

The present study demonstrates that dexmedetomidine preserves flow to the most vital organs (brain, heart, liver, kidneys) at the expense of less vital organs and flow through arteriovenous shunts. Oxygen consumption of the body decreased only in the CU group. Baseline oxygen uptake was 39% higher in the CU group than in the FH group ($P = 0.056$). This difference may be due to a higher sympathetic activity, known to occur during CU anesthesia [10]. The finding that the decreased oxygen uptake in this group was accompanied by a lower arterial lactate concentration argues against the occurrence of major ischemia in any organ. Rather, it indicates that dexmedetomidine decreased the oxygen requirements of the body. Blood flow in the vital organs remained well above the levels known to induce underperfusion, supporting the idea that the redistribution of cardiac output induced by dexmedetomidine is appropriate. The decrease in blood flow in organs with low oxygen extraction appears an important contributor to the increase in mixed venous oxygen extraction.

The larger decrease in blood flow to the left ventricle in the CU than in the FH dogs can be explained by a greater myocardial energy-saving effect of dexmedetomidine in the former group [2]. In this earlier study little change in arteriocoronary oxygen saturation difference was observed after dexmedetomidine in either anesthesia group, indicating that most of the reduction in myocardial blood flow was due to metabolic regulation of the myocardium rather than adrenergic vasoconstriction [2].

The finding that CBF decreased only in the FH group (especially those with the high baseline values) may be explained by relative vasodilation in these experiments, a well-known side effect of halothane [11]. Of note, dexmedetomidine reduced CBF to a level similar to that observed in the CU group and to values usually found in conscious dogs [12]. In dog studies which have shown a decrease in sagittal sinus flow, either isoflurane [13] or halothane [14] was used as anesthetic. The larger decline in these studies might be explained by the fact that sagittal sinus outflow includes shunt flow. This idea is supported by the absence of changes in cerebral oxygen consumption [13,14].

The decrease in renal blood flow is in accordance with the findings of de Leeuw *et al.* [15], who showed an increase of renal blood flow by administration of α_2-adrenergic antagonists in the renal artery of hypertensive patients.

The decrease of cutaneous blood flow by dexmedetomidine is in agreement with findings on finger blood flow after administration of clonidine in human subjects, as measured by plethysmography [16]. This technique measures gross blood flow, including flow through arteriovenous anastomoses. In extremities, shunt flow accounts for a considerable part of total blood flow and the role of α_2-adrenoceptors in regulation of shunt flow is well known [17].

Liver blood flow as measured with microspheres represents only flow through the hepatic artery [18] and does not take into account portal venous flow. Since intestinal

flow did not change but shunt flow decreased considerably, dexmedetomidine may have decreased total blood flow through the liver to some extent.

The absolute contribution of each organ to the redistribution of CO requires knowledge of the size of these organs. With a body surface of approximately 1 m^2, the weight of the skin is approximately 5 kg, so that the reduction of cutaneous flow of 4 $mL \cdot min^{-1} \cdot 100\ g^{-1}$ amounts to a total reduction of 200 mL/min. Similarly, with lung and kidney weights of 300 and 200 g, respectively, total "lung" flow, representing arteriovenous shunt flow, and renal flow amount to decreases of about 150 and 200 mL/min, respectively. While blood flow to these three organs can explain a decrease of about one third of the decrease in CO, all remaining organs make up the rest of the decrease.

We used dogs for this study, since the microsphere method is not applicable in man. Because animals have different sensitivity to anesthetics than man, the anesthetic regimen used is of limited clinical importance. Anesthesia was initially induced with thiopental, a barbiturate with a half-life of approximately 20 min in dogs. This was used to tracheally intubate the animals and subsequently start the two anesthetic regimens. The actual measurements occurred two to three hours after induction of anesthesia, so that the effect of this anesthetic had expired, and only the effects of the FH or CU anesthesia prevailed.

Chloralose and urethane (ethyl carbamate) are used as anesthetics for acute animal experiments especially because they have few effects on cardiac function [19] and cardiovascular reflexes [20]. Urethane activates the sympathetic outflow from the central nervous system [10]. Halothane depresses baroreflex activity [21] and reduces contractility [22], heart rate, and blood pressure [23]. Fentanyl increases vagal tone [24] and reduces sympathetic tone [25]. Using these two anesthetic regimens we obtained two groups of animals with considerably different baseline conditions, which allowed us to study the extent that differences in such conditions could affect the influence of dexmedetomidine on organ flow. Although the CU regimen is not directly applicable clinically, this study shows that dexmedetomidine's effect on organ flow is not much affected by the type of anesthesia, a conclusion with clinical relevance. The present study only focused on the effects of dexmedetomidine on organ flow under near optimal baseline conditions. Further studies are required to determine the effects of dexmedetomidine administration when the circulation is already compromised.

Summarizing, dexmedetomidine decreased blood flow to most organs, but the largest decrease occurred in skin, spleen, and in arteriovenous shunts. Mixed venous oxygen extraction increased and oxygen uptake remained constant (FH) or decreased to a limited extent (CU). Perfusion of vital organs such as the heart, brain, and kidneys was only moderately reduced, which could also be explained by functional alterations in these organs. Overall adequacy of oxygen supply to the body was indicated by unchanged (FH) or lowered (CU) arterial plasma lactate concentrations, even at the highest (10 μg/kg, supraclinical) dose of dexmedetomidine.

The results in the present study were obtained in healthy dogs with a well maintained anesthesia, cardiac function, and preload. Dexmedetomidine's effect on organ flow has not been assessed under less optimal conditions.

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References

1 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605.
2 Lawrence CJ, Prinzen FW, de Lange S. The Effect of dexmedetomidine on the balance of myocardial energy requirement and oxygen supply and demand. *Anesth Analg* 1996; **82**: 544–50.
3 Roekaerts PM, Willigers HMM, Prinzen FW, Lange S. The effects of alpha$_2$-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs. *Anesth Analg* 1996; **82(4)**: 702–11.
4 Roekaerts PMHJ, Prinzen FW, de Lange S. Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1996; **10**: 619–26.
5 Flacke WE, Flacke JW, Bloor BC, *et al.* Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7(1)**: 41–9.
6 Proctor LT, Schmeling WT, Roerig D, *et al.* Oral dexmedetomidine attenuates hemodynamic responses during emergence from general anesthesia in chronically instrumented dogs. *Anesthesiology* 1991; **74(1)**: 108–14.
7 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77(6)**: 1134–42.
8 Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labeled microspheres. *Prog Cardiovasc Dis* 1977; **20**: 55–79.
9 Prinzen FW, Van der Vusse GJ, Reneman RS. Blood flow distribution in the left ventricular free wall in open-chest dogs. *Basic Res Cardiol* 1981; **76**: 431–7.
10 Maggi CA, Meli A. Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 1: General considerations. *Experientia* 1986; **42(2)**: 109–14.
11 Wollman H, Alexander SC, Cohen PJ, *et al.* Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and δ-tubocurarine. *Anesthesiology* 1964; **25**: 180–4.
12 Haberer JP, Audibert G, Saunier CG, *et al.* Effect of propofol and thiopentone on regional blood flow in brain and peripheral tissues during normoxia and hypoxia in the dog. *Clin Physiol* 1993; **13(2)**: 197–207.
13 Zornow MH, Fleischer JE, Scheller MS, *et al.* Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesth Analg* 1990; **70(6)**: 624–30.
14 Karlsson BR, Forsman M, Roald OK, *et al.* Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs [see comments]. *Anesth Analg* 1990; **71(2)**: 125–9.
15 de Leeuw PW, van Es PN, de Bos R, Birkenhager WH. Role of alpha 1- and alpha 2-adrenergic receptors in the human hypertensive kidney. *Hypertension* 1987; **9**: 1210–2.

16 Coffman JD, Cohen RA. Role of alpha-adrenoceptor subtypes mediating sympathetic vasoconstriction in human digits. *Eur J Clin Invest* 1988; **18(3)**: 309–13.
17 Baker CH, Davis DL, Sutton ET. Blood flow distribution with adrenergic and histaminergic antagonists. *Proc Soc Exp Biol Med* 1989; **190(3)**: 260–7.
18 Daemen MJAP, Thijssen HHW, Essen Hv, *et al.* Liver blood flow measurement in the rat. The electromagnetic versus the microsphere and the clearance methods. *J Pharmacol Methods* 1989; **21**: 287–97.
19 Lang RM, Marcus RH, Neumann A, *et al.* A time-course study of the effects of pentobarbital, fentanyl, and morphine chloralose on myocardial mechanics. *J Appl Physiol* 1992; **73(1)**: 143–50.
20 Maggi CA, Meli A. Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 2: Cardiovascular system. *Experientia* 1986; **42(3)**: 292–7.
21 Seagard JL, Hopp FA, Donegan JH, *et al.* Halothane and the carotid sinus reflex: evidence for multiple sites of action. *Anesthesiology* 1982; **57**: 191–202.
22 Trigt vP, Christian CC, Fagraeus L, *et al.* Myocardial depression by anesthetic agents (halothane, enflurane and nitrous oxide): quantitation based on end-systolic pressure-dimension relations. *Am J Cardiol* 1984; **53(1)**: 243–7.
23 Wilkinson PL, Tyberg JV, Moyers JR, White AE. Correlates of myocardial oxygen consumption when afterload changes during halothane anesthesia in dogs. *Anesth Analg* 1980; **59**: 233–9.
24 Inoue K, Samodelor LF, Arndt JO. Fentanyl activates a particular population of vagal efferentes which are cardioinhibitory. *Naunyn-Schmiedebergs Arch Pharmacol* 1980; **312(1)**: 57–61.
25 Laubie M, Schmitt H, Drouillat M. Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic agent fentanyl. *Naunyn-Schmiedebergs Arch Pharmacol* 1977; **296**: 255–61.

CHAPTER 7

Hemodynamic and coronary vascular effects of dexmedetomidine in the anesthetized goat†

C. J. Lawrence, F. W. Prinzen, and S. de Lange

In phase III trials, the hemodynamic stabilising effect of the α_2-adrenergic agonist dexmedetomidine is being investigated in patients with coronary artery disease. Coronary vascular effects of α_2-agonists have been studied in dogs and pigs, but both species have a different hemodynamic response to dexmedetomidine than man. The aim of this study was to investigate the hemodynamic and coronary vascular effects in goats. In six open-chest goats anesthetized with halothane, central and coronary hemodynamics and oxygen supply and demand were measured before and following IV bolus infusion of dexmedetomidine in doses ranging from 0.1 to 10 μg/kg. With dexmedetomidine doses of 1 μg/kg or higher, mean arterial pressure (MAP), systemic vascular resistance, coronary vascular resistance, and arterio-mixed venous oxygen content increased within 2 min, but returned to baseline within 15 min. In contrast, there was a progressive and cumulative decrease in cardiac output (CO), heart rate, and the first positive derivative of left ventricular pressure (dP/dt_{max}). Regional coronary venous oxygen extraction ($C(a\text{-}cv)o_2$) transiently increased after 3 μg/kg dexmedetomidine and decreased 15 min after 10 μg/kg dexmedetomidine. Left ventricular end-diastolic pressure transiently increased after 3 and 10 μg/kg dexmedetomidine. The changes after dexmedetomidine 10 μg/kg differed from those after lower doses: MAP (35%), CO (50%), stroke volume (33%), $C(a\text{-}cv)o_2$ (15%), and myocardial oxygen extraction (33%) were all decreased. Myocardial oxygen supply and demand decreased in parallel. We conclude that (1) the cardiovascular response to IV dexmedetomidine in goats is similar to man, (2) in goats after dexmedetomidine, systemic and coronary vasoconstriction are short lived, and (3) the balance between myocardial oxygen supply and demand is maintained.

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Introduction

α_2-Adrenergic agonists have been shown to produce sedation, analgesia, and reduction of anesthetic requirements together with increased hemodynamic stability in animals and man [1]. The selective α_2-adrenergic agonists like dexmedetomidine seem to be more promising than clonidine in this respect [2,3]. In man, the hemodynamic effects of dexmedetomidine are biphasic: a rapid transient increase in mean arterial pressure (MAP) and systemic vascular resistance (SVR), accompanied by a reduction in heart rate (HR), followed within 15 min by a decrease in contractility and MAP [4]. The former is caused by stimulation of postsynaptic vascular receptors, whereas central α_2-adrenergic receptors, by decreasing sympathetic activity and stimulating parasympathetic activity, are involved in the latter changes [5]. In contrast, studies in anesthetized dogs showed a sustained increase in blood pressure with systemic and coronary vasoconstriction after IV administration of dexmedetomidine [6,7], and it has been suggested that the coronary vasoconstriction may lead to myocardial ischemia [7]. Similar species differences may be present for the degree of α_2-adrenergic coronary vasoconstriction. Dexmedetomidine IV increased coronary vascular resistance by up to 45% in dogs [8]. In man, Indolfi *et al.* demonstrated an α_2-adrenergic-agonist-induced decrease in coronary artery diameter and flow velocity of approximately 28% [9]. On the other hand, Schulz *et al.* demonstrated that there are no α_1- and relatively little α_2-adrenoceptor mediated coronary constrictive effects in pigs [10]. Better understanding of the coronary vascular effects of α_2-adrenergic agonists is required because phase III trials are being carried out in patients with coronary artery disease. Since studies on coronary flow and oxygen consumption can be performed in more detail in experimental animals, we looked for a species whose response to α_2-adrenergic agonists was more similar to that observed in man.

Pilot experiments in anesthetized goats in our laboratory showed that the hypertensive phase after dexmedetomidine was shorter than in anesthetized dogs, and more like that seen in man. Therefore, we studied the effects of dexmedetomidine on systemic and coronary hemodynamics in goats, paying special attention to the balance between myocardial oxygen supply and demand. For this purpose a range of IV doses of dexmedetomidine were administered to anesthetized open-chest goats.

Methods

Approval for the study was obtained from the local animal ethical committee prior to commencing the experiments. Six goats weighing 25–50 kg were used for the study. The goats were anesthetized with sodium thiopental 20 mg/kg IV. After intubation, the animals were ventilated with a mixture of oxygen 40% and nitrous oxide 60% to maintain end-expired carbon dioxide concentration between 3.5 and 4.5 kPa. Anesthesia was maintained by adding halothane 1–2% to the nitrous oxide anesthesia.

Oxygen saturation was monitored by pulse oximetry and arterial blood gases were frequently analyzed during the study (ABL 3, Radiometer, Copenhagen, Denmark). The temperature was recorded and maintained as close as possible to 38°C by means of a heating pad under the animal. A venous cannula was inserted in a leg vein for infusion of fluids and medication. A femoral artery was surgically exposed and a long catheter for arterial blood sampling and measurement of arterial pressure (catheter-tip transducer, Millar Instruments Inc, Houston, Texas, U.S.A.) introduced into the aorta. The thorax was opened via the 5th lateral intercostal space and the pericardium opened to expose the heart. The left circumflex coronary artery was prepared and a flow probe (Skalar, Delft, The Netherlands) placed around it near its origen. A small polyethelene catheter (PE 60) was inserted into the coronary vein accompanying the artery in order to obtain regional venous blood samples. A catheter-tip transducer (Millar) was inserted into the left ventricle (LV) via the left common carotid artery or the right femoral artery. The first positive derivative of left ventricular pressure (dP/dt_{max}) and heart rate were derived from the left ventricular pressure signal. A thermodilution pulmonary artery catheter was used to obtain mixed venous blood samples from the pulmonary artery and to measure cardiac output by the thermodilution technique. Left ventricular pressure, aortic pressure, coronary flow, and ECG (lead II) were continuously displayed (Knott GS-8 Monitor, Knott Electronik, Hohen Schäftlarn, Germany). All pressures and flows were recorded continuously using a pen-recorder (Schwarzer RE 412 recorder, München, Germany) at 0.25 cm · s^{-1} with the speed increased to 5 cm · s^{-1} during data aquisition.

Dexmedetomidine was supplied by Orion Corp., Farmos, Turku, Finland as a crystalline powder. This was dissolved in saline to produce a solution containing 100 μg/mL. The calculated dose was taken from this solution using a 1-mL syringe, transferred to a 20-mL syringe, and diluted to 20 mL with 0.9% sodium chloride solution before injection. All test medications were given (over 2 min using a perfusor) into the right atrium through the right atrium port of the pulmonary artery catheter.

After completion of instrumentation and a stabilisation period of 15 min baseline measurements were taken. Following this, incremental doses of dexmedetomidine (0.1, 0.3, 1, 3, and 10 μg/kg) were given and measurements repeated at peak mean blood pressure effect (within 1–2 min), and 15 min later. At each measurement point the following data were obtained: heart rate (HR), mean arterial pressure (MAP), left ventricular end-diastolic pressure (LVEDP), circumflex coronary artery blood flow (CF), dP/dt_{max}, and thermodilution cardiac output (CO). Arterial, mixed venous (pulmonary artery), and coronary venous blood was collected for measurement of hemoglobin and blood gases (ABL 3, blood gas analyzer, OSM 2 hemoximeter saturation analyzer, Radiometer, Copenhagen, Denmark). After completion of the 15 min measurements, the next dose of dexmedetomidine was given.

Systemic vascular resistance (SVR) and coronary vascular resistance (CVR) were calculated using the formulae below:

$$SVR = MAP \times 80 / CO \ (dynes \cdot s \cdot cm^{-5})$$

$$CVR = MAP / CF \ (mm\ Hg \cdot mL^{-1} \cdot min^{-1})$$

Stroke Work (SW) was calculated as:

$$SW = MAP \times SV \ (mL \cdot mm\ Hg)$$

where SV is stroke volume. Mixed venous oxygen extraction (mL/dL blood) was calculated as:

$$Hb \times 1.34 \times (Sao_2 - Svo_2)$$

where

Hb = hemoglobin (g/dL)
Sao_2 = arterial oxygen saturation
Svo_2 = mixed venous oxygen saturation.

Total body oxygen uptake (mL/min) was calculated as:

$$CO \times Hb \times 1.34 \times (Sao_2 - Svo_2)$$

where CO is cardiac output. Regional coronary venous oxygen extraction (mL/dL blood) as:

$$Hb \times 1.34 \times (Sao_2 - Scvo_2)$$

where $Scvo_2$ is regional coronary venous oxygen saturation. Myocardial oxygen uptake (MVo_2, mL/min) in the region supplied by the left circumflex artery was calculated as:

$$CF \times Hb \times 1.34 \times (Sao_2 - Scvo_2)$$

where CF is coronary flow (left circumflex artery).

Analysis of variance for repeated measures (RM ANOVA) was used for statistical comparison. If the response over all data points showed a significant difference then each post-dexmedetomidine value was separately compared with baseline, and each peak value with preceding "recovery" value. $P < 0.05$ was considered significant.

Table 7-1 Effects of dexmedetomidine on hemodynamics and oxygen extraction in goats

Variable	Baseline	Dexmedetomidine dose (μg/kg)				
		0.1		0.3		1.0
		peak	15 min	peak	15 min	peak
CO (L/min)	2.95 ± 0.43	2.76 ± 0.44	2.83 ± 0.45	2.66 ± 0.44	2.92 ± 0.47	2.35 ± 0.43*†
LVEDP (mm Hg)	7.50 ± 0.58	7.42 ± 0.87	6.67 ± 0.58	8.73 ± 1.27	8.37 ± 0.57	10.21 ± 2.23
SV (mL)	31.34 ± 5.19	30.78 ± 5.41	32.02 ± 5.44	31.63 ± 5.25	34.24 ± 5.92	29.49 ± 4.72
SW (mL · mm Hg)	2987 ± 446	2946 ± 626	2555 ± 459	3256 ± 793	2893 ± 642	3508 ± 642
DP/dt_{max} (mm Hg/s)	1628 ± 208	1472 ± 173	1496 ± 193	1439 ± 183*	1492 ± 168	1402 ± 180*
$C(a\text{-}v)O_2$ (mL/dL)	4.69 ± 0.38	4.59 ± 0.48	4.51 ± 0.52	5.00 ± 0.30	4.06 ± 0.42	6.35 ± 0.93*†
VO_2 (mL/min)	137.80 ± 22.38	123.17 ± .23	125.68 ± 25.45	130.57 ± 22.21	118.64 ± 24.41	147.96 ± 36.33
MVO_2 (mL/min)	2.88 ± 0.87	2.56 ± 0.58	2.41 ± 0.70	2.94 ± 0.89	2.26 ± 0.68	2.65 ± 0.67

	1.0	3.0		10.0	
	15 min	peak	15 min	peak	15 min
CO (L/min)	2.43 ± 0.44*	1.84 ± 0.34*†	2.14 ± 0.41*	1.43 ± 0.26*†	1.41 ± 0.31*
LVEDP (mm Hg)	8.08 ± 0.88	12.62 ± 1.37*†	9.68 ± 1.31†	13.88 ± 1.50*†	8.83 ± 1.13†
SV (mL)	30.30 ± 5.02	25.42 ± 4.55*	29.40 ± 5.01	21.81 ± 4.22*†	22.02 ± 5.21*
SW (mL · mm Hg)	2414 ± 481†	3013 ± 558	2180 ± 551	2512 ± 710	1522 ± 484*†
DP/dt_{max} (mm Hg/s)	1287 ± 160*	1310 ± 174*	1104 ± 171*†	1034 ± 185*	746 ± 142*†
$C(a\text{-}v)O_2$ (mL/dL)	5.21 ± 0.93	6.38 ± 0.66*	4.99 ± 0.55	7.05 ± 0.48*†	6.60 ± 0.43*
VO_2 (mL/min)	132.03 ± 39.84	109.68 ± 16.42	102.41 ± 22.15	99.91 ± 19.70	90.22 ± 18.98
MVO_2 (mL/min)	2.06 ± 0.60*	2.45 ± 0.67	2.45 ± 0.84	2.32 ± 0.64	1.91 ± 0.56*

Values are expressed as mean ± SEM and are measured at baseline and after dexmedetomidine in the doses shown. peak = at the time of peak effect on mean arterial pressure; 15 min = 15 min after "peak" effect; CO = cardiac output; LVEDP = left ventricular end-diastolic pressure; SV = stroke volume; SW = stroke work; dP/dt_{max} = first positive derivative of left ventricular pressure; $C(a\text{-}v)O_2$ = arterio-mixed venous oxygen content difference; VO_2 = total body oxygen consumption; MVO_2 = myocardial oxygen uptake in the region supplied by the left circumflex coronary artery. * = Significantly different ($P < 0.05$) from baseline. † = Significantly different ($P < 0.05$) from previous value. (Repeated Measures ANOVA – see Methods).

Results

MAP increased after each dose of dexmedetomidine except the lowest, this rise being significant when compared to the preceding "recovery" value. However, only after the 1 and 3 μg/kg dose was MAP significantly increased with respect to baseline. Fifteen minutes later, MAP had fallen below baseline, this decrease being significant after 10 μg/kg (Figure 7-1). The acute MAP rise following each dose (δMAP) increased until 1 μg/kg and then remained constant. SVR increased significantly from the previous "recovery" value following dexmedetomidine 1, 3, and 10 μg/kg, and these "peak" values were significantly different from baseline. Fifteen minutes after each of these doses, SVR had decreased to values which were not significantly different from baseline (Figure 7-2). As with δMAP, the maximum acute rise in SVR (δSVR) occurred after 1 μg/kg of dexmedetomidine whereafter it remained constant. HR (Figure 7-1) and CO (Table 7-1) declined dose-dependently reaching significance after 0.1 and 1 μg/kg, respectively, and showing no recovery 15 min later. SV was reduced

2 min following 3 and 10 μg/kg dexmedetomidine but recovered within 15 min except at the highest dose (Table 7-1).

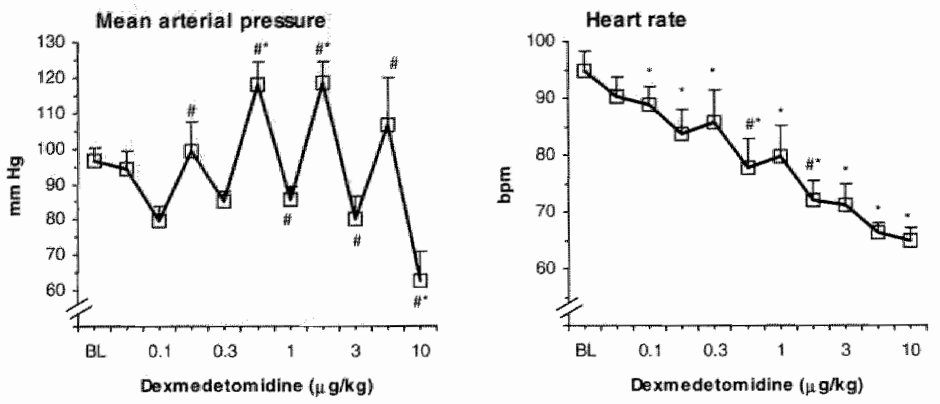

Figure 7-1 Effects of incremental doses of dexmedetomidine injected intravenously over 2 min in the doses shown on mean arterial blood pressure (left panel) and heart rate (right panel) in anesthetized goats. BL = Baseline. For each dose of dexmedetomidine the value at peak blood pressure effect (within 2 min) and the effect after 15 min are shown. Values are mean ± SEM. * Significantly different ($P < 0.05$) from baseline. # Significantly different ($P < 0.05$) from previous value. (Repeated Measures ANOVA – see Methods).

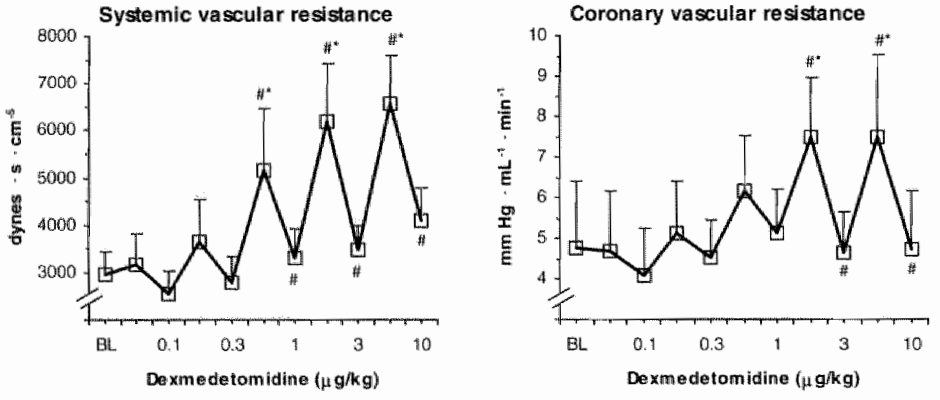

Figure 7-2 Effects of incremental doses of dexmedetomidine injected intravenously over 2 min in the doses shown on systemic vascular resistance (left panel) and coronary vascular resistance (right panel) in anesthetized goats. BL = Baseline. For each dose of dexmedetomidine the value at peak blood pressure effect (within 2 min) and the effect after 15 min are shown. Values are mean ± SEM. * Significantly different ($P < 0.05$) from baseline. # Significantly different ($P < 0.05$) from previous value. (Repeated Measures ANOVA – see Methods).

LVEDP increased significantly following 3 and 10 μg/kg dexmedetomidine but recovered within 15 min (Table 7-1). SW was significantly reduced 15 min after 10 μg/kg dexmedetomidine (Table 7-1). $LVdP/dt_{max}$ declined dose-dependently; following 1, 3, and 10 μg/kg dexmedetomidine the 15 min value was lower than the "peak" effect (Table 7-1). Mixed venous oxygen extraction increased dose-dependently (significant after dexmedetomidine 1, 3, and 10 μg/kg) showing recovery except after dexmedetomidine 10 μg/kg (Table 7-1). In spite of this increase in extraction, oxygen consumption (VO_2) declined, though this was not significant (P = 0.058, Table 7-1).

CVR increased immediately after dexmedetomidine 3 and 10 μg/kg but returned to baseline within 15 min (Figure 7-2). The acute rise in CVR following each dose of dexmedetomidine (δCVR) increased until 3 μg/kg and then remained constant. Coronary flow showed a gradual decrease, which did not reach the level of significance (Figure 7-3). Regional coronary venous oxygen extraction increased immediately following dexmedetomidine only after the 3 μg/kg dose but fell to below baseline 15 min after the 10 μg/kg dose (Figure 7-3). Fifteen minutes following dexmedetomidine 1 and 10 μg/kg, regional myocardial oxygen consumption was significantly reduced.

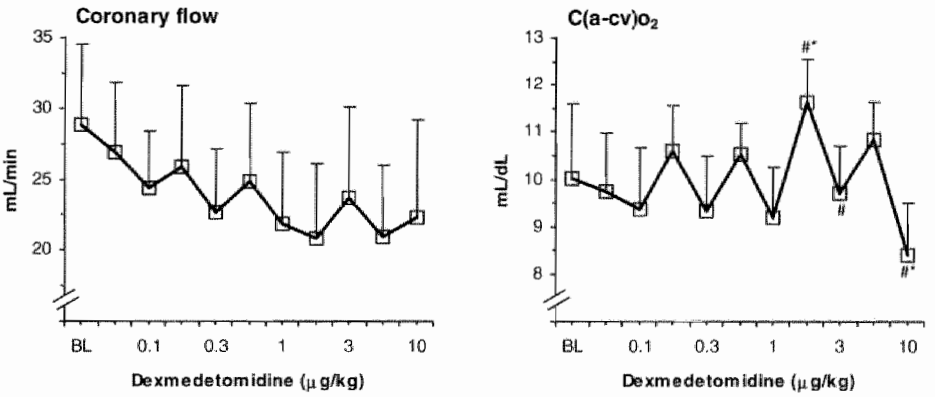

Figure 7-3 Effects of incremental doses of dexmedetomidine injected intravenously over 2 min in the doses shown on coronary blood flow (left panel) and arterio-regional coronary venous oxygen content difference (right panel) in anesthetized goats. BL = Baseline. For each dose of dexmedetomidine the value at peak blood pressure effect (within 2 min) and the effect after 15 min are shown. Values are mean ± SEM. * Significantly different ($P < 0.05$) from baseline. # Significantly different ($P < 0.05$) from previous value. (Repeated Measures ANOVA – see Methods).

Discussion

The main conclusions of this study are:

1. In goats, IV administration of dexmedetomidine causes a rapid short-lived increase in blood pressure and SVR, followed within 15 min by a decrease in blood pressure and accompanied by progressively decreasing HR and CO, similar to the hemodynamic effects seen in man.
2. Systemic and coronary vasoconstriction are short-lived, even at the relatively high dose of 10 μg/kg.
3. The balance between myocardial oxygen supply and demand may be better maintained in goats than in dogs.

Hemodynamic effects

In studies of the hemodynamic effects of dexmedetomidine in man, the subjects have all received dexmedetomidine while still awake. In conscious human volunteers, following a 2 μg/kg IV dose of dexmedetomidine, MAP increased initially (max at 3 min) and then decreased, remaining significantly lower (± 17%) during the 330 min of the experiment; CO and HR were also decreased [4]. In anesthetized dogs, however, a long-lasting increase in SVR is observed resulting in sustained hypertension in spite of reductions in HR and CO [6–8].

A difference between anesthetics in the modulation of dexmedetomidine-responses has been suggested [11], and we have previously shown that the hemodynamic response to dexmedetomidine is influenced by anesthetic technique in a dog model [8]. Specifically, halothane has been shown to reduce the pressor effect following dexmedetomidine in dogs [12] while fentanyl augments the bradycardic but not the pressor effects of dexmedetomidine [13]. Although the anesthetic may influence an animal's response to dexmedetomidine, in this goat study we used halothane, the same as was used in our previous dog investigation [8]. The present study shows that the hemodynamic response of goats to IV administration of dexmedetomidine is more similar to that seen in conscious man.

In the present study, peak values of SVR at the various doses were similar to those of dogs under enflurane [7] or halothane anesthesia [8]. This suggests that the different response in goats is not due to a different number of (active) vascular α_2-adrenergic receptors. Moreover, the decrease in HR and CO was similar in these studies, indicating that the stimulation of the central α_2-adrenergic receptors was similar and that there was no major difference in clearance of the drug. The more rapid disappearance of the pressor effect in goats could then be caused by a more rapid distribution of dexmedetomidine in the body of the goats which might affect the peripheral more than the central actions.

In studies by Jalonen *et al.* in anesthetized young domestic pigs, MAP increased by 45% within 2 min of a rapid (5 s) IV injection of dexmedetomidine 10 μg/kg but returned to baseline within 15 min. There was no decrease in CO and only a transient slight (11%) decrease in HR [14]. Therefore, the pig seems to behave completely differently from other species with respect to its hemodynamic response to α_2-agonists.

It should be mentioned that beside species differences and anesthetic technique other factors may influence the hemodynamic response to α_2-agonists. A slower rate of infusion [15], oral administration [16,17], or intramuscular administration [18] reduces or avoids the pressor effect.

The small number of animals studied (6) may be the reason that some effects did not reach significance, for example, CF and VO_2. However, most parameters changed quite reproducably from animal to animal. We did not include a control group because in previous dog studies, using similar preparation and anesthesia, the preparation was stable for several hours [19]. Since the protocol started some hours after the onset of anesthesia and ventilation, a steady state situation had been reached so that we primarily measured the effects of the drug. Throughout the surgical preparation and study protocol we paid special attention to maintaining constant temperature, respiratory and metabolic status as well as correcting blood and fluid losses.

The highest dose of dexmedetomidine was followed by effects not seen at lower doses: MAP decreased to about 60 mm Hg, myocardial oxygen extraction was 15% below baseline (Figure 7-3), CO was 50% and SV 33% below baseline, while MVO_2 was 30% reduced (Table 7-1). This indicates a marked inhibition of sympathetic outflow, which is probably favorable in view of the reduced vascular resistance, myocardial contractility, and oxygen extraction. The transiently increased LVEDP following 3 and 10 μg/kg dexmedetomidine does suggest some impairment of cardiac function probably due to the acute increase in afterload, but this is short-lived. This is in contrast to the effects seen in dogs where both MAP and SVR remain significantly elevated above baseline, thereby increasing the work of the heart.

Coronary vascular effects

In the only study on the human coronary circulation, intracoronary infusion of azepexole decreased coronary artery diameter and blood flow velocity by 28% [9].

Swine have been shown to exhibit hardly any α_2- or α_1-adrenoceptor-mediated coronary vasoconstriction [10]. Accordingly, Bloor and Fonarow did not observe any significant increase in coronary vascular resistance after intracoronary infusion of dexmedetomidine at a rate of up to 40 μg/min in anesthetized minipigs [20]. Also, Jalonen *et al.* found only a moderate (15%) increase in regional coronary resistance in anesthetized young pigs after rapid IV injection of 30 μg/kg dexmedetomidine [14].

In contrast, sustained α_2-adrenergic coronary vascular vasoconstriction has been shown in dogs [21,22]. Our previous dog study demonstrated a transient increase in coronary vascular resistance by up to 45%. A sustained increase in CVR as well as myocardial oxygen consumption occurred only at a dose of 10 μg/kg and this effect was independent of the anesthesia used. [8]. Moreover, no change in lactate extraction occurred, indicating the absence of ischemia. Savola *et al.* gave IV infusions of dexmedetomidine to enflurane-anesthetized dogs and found marked increases in systemic arterial pressure but no effect on coronary blood flow, as measured by positron emission tomography [23]. Also, in conscious, chronically-instrumented dogs 5 μg/kg dexmedetomidine IV over 10 min did not change coronary flow velocity, but increased coronary resistance [24].

In the present study in goats, CVR increased by up to 57%. In contrast to dogs [8], CVR and myocardial oxygen extraction rapidly returned to baseline and, after dexmedetomidine 10 μg/kg, even decreased. This indicates that regulation of myocardial blood flow occurs through metabolic regulation rather than adrenergic stimulation [25]. The reduction in myocardial oxygen demand is most likely related to the central autonomic effects of dexmedetomidine, causing decreases in HR, contractility and MAP.

In conclusion, the present study shows that the systemic vascular effect of dexmedetomidine in man resembles that of goats better than dogs and that the balance between myocardial oxygen supply and demand may be better maintained in goats than in dogs. It is interesting that in dogs beneficial effects of clonidine, dexmedetomidine, and mivazerol on ischemic myocardium have been observed [19,26,27]. This indicates that further investigation of the anti-ischemic effects of α_2-adrenergic agonists in goats as well as in man is worthwhile.

Acknowledgments

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References

1 Maze M, Tranquilli W. α_2-adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605.

2 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an α_2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5.

3 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992; **75**: 940–6.

4 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42.

5 Bloor BC, Schmeling WT. Cardiovascular effects of α_2-adrenoceptors. *Anesth Pharm Rev* 1993; **1**: 246–62.

6 Bloor BC, Frankland M, Alper G, Raybould D, Weitz J, Shurtliff M. Hemodynamic and sedative effects of dexmedetomidine in dog. *J Pharmacol Exp Ther* 1992; **263**: 690–7.

7 Flacke WE, Flacke JW, Bloor BC, McIntee DF, Sagan M. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7**: 41–9.

8 Lawrence CJ, Prinzen FW, de Lange S. The effect of dexmedetomidine on the balance of myocardial energy requirement and oxygen supply and demand. *Anesth Analg* 1996; **82**: 544–50.

9 Indolfi C, Piscioni F, Villari B, Russolillo E, Rendina V, Golino P, *et al.* Role of α_2-adrenoceptors in normal and atherosclerotic human coronary circulation. *Circulation* 1992; **86**: 1116–24.

10 Schulz R, Oudiz RJ, Guth BD, Heusch G. Minimal AA1- and AA2-adrenoceptor-mediated coronary vasoconstriction in the anaesthetized swine. *Naunyn-Schmiedebergs Arch Pharmacol* 1990; **342**: 422–8.

11 Scheller MS, Zornow MH. Are the hemodynamic effects of dexmedetomidine influenced by the background anesthetic? (letter; comment). *Anesth Analg* 1991; **72**: 408–9.

12 Kenny D, Pelc LR, Brooks HL, Kampine JP, Schmeling WT, Warltier DC. Calcium channel modulation of α_1- and α_2-adrenergic pressor responses in concious and anesthetized dogs. *Anesthesiology* 1990; **72**: 874–81.

13 Salmenperä MT, Szlam F, Hug CJ. Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. *Anesthesiology* 1994; **80**: 837–46.

14 Jalonen J, Halkola L, Kuttila K, Perttila J, Rajalin A, Savunen T, *et al.* Effects of dexmedetomidine on coronary hemodynamics and myocardial oxygen balance. *J Cardiothorac Vasc Anesth* 1995; **9**: 519–24.

15 Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, *et al.* Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology* 1995; **82**: 620–33.

16 Proctor LT, Schmeling WT, Roerig D, Kampine JP, Warltier DC. Oral dexmedetomidine attenuates hemodynamic responses during emergence from general anesthesia in chronically instrumented dogs. *Anesthesiology* 1991; **74**: 108–14.

17 Proctor LT, Schmeling WT, Warltier DC. Premedication with oral dexmedetomidine alters hemodynamic actions of intravenous anesthetic agents in chronically instrumented dogs. *Anesthesiology* 1992; **77**: 554–62.

18 Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; **78**: 813–20.

19 Roekaerts PM, Prinzen FW, Willigers HM, De Lange S. The effects of α_2-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs. *Anesth Analg* 1996; **82**: 702–11.

20 Bloor B, Fonarow G. Intracoronary dexmedetomidine does not produce coronary vasoconstriction at therapeutic blood levels in chronically instrumented anaesthetized swine. *J Cardiothorac Vasc Anesth* 1994; **8** (5, Suppl 3): 4.

21 Holtz J, Saeed M, Sommer O. Norepinephrine constricts the canine coronary bed via postsynaptic α_2-adrenoceptors. *Eur J Pharmacol* 1982; **82**: 199–202.

22 Deussen A, Heusch G, Thämer V. α_2-adrenoceptor-mediated coronary vasoconstriction persists after exhaustion of coronary vasodilator reserve. *Eur J Pharmacol* 1985; **115**: 147–53.

23 Savola J, Brennan K, Maze M, Stalnaker C, Budinger T. No decrease in myocardial blood flow during infusion of dexmedetomidine as assessed using positron emission tomography in anaesthetized dogs. *Eur J Pharmacol* 1990; **183**: 360–1.

24 Schmeling WT, Kampine JP, Roerig DL, Warltier DC. The effects of the stereoisomers of the α_2-adrenergic agonist medetomidine on systemic and coronary hemodynamics in conscious dogs. *Anesthesiology* 1991; **75**: 499–511.
25 Mohrman DE, Feigl EO. Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. *Circ Res* 1978; **42**: 79–86.
26 Heusch G, Schipke J, Thamer V. Clonidine prevents the sympathetic initiation and aggravation of poststenotic myocardial ischemia. *J Cardiovasc Pharmacol* 1985; **7**: 1176–82.
27 Roekaerts PMHJ, Prinzen FW, de Lange S. Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1996; **10**: 619–26.

CHAPTER 8

Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative hemodynamic stability†

C. J. Lawrence and S. de Lange

In a double-blind, placebo-controlled study we investigated the effect of a single pre-induction intravenous dose of dexmedetomidine 2 μg/kg on anesthetic requirements and peri-operative hemodynamic stability in 50 patients undergoing minor orthopedic and general surgery. Patients were anesthetised with nitrous oxide/oxygen/fentanyl, supplemented if necessary with isoflurane. The mean (± SD) intra-operative isoflurane concentration was lower in dexmedetomidine-treated patients than controls (0.01 ± 0.03% compared to 0.1 ± 0.1%; $P = 0.001$) although six of the 25 treated patients required isoflurane at some stage. The hemodynamic response to tracheal intubation and extubation was reduced in the dexmedetomidine group as was intra-operative heart rate variability; postoperative analgesic and anti-emetic requirements and peri-operative serum catecholamine concentrations were lower in the dexmedetomidine group. Hypotension and bradycardia occurred more frequently after dexmedetomidine.

Introduction

α_2-Adrenergic agonists are of interest to anesthetists because of their ability to produce sedation, anxiolysis and analgesia. They have also been reported to reduce anesthetic requirements and afford hemodynamic and sympathetic stability during the intra-operative period [1,2]. Clonidine has been shown to increase hemodynamic stability [3,4] and reduce anesthetic requirements in a variety of clinical situations [5,6].

Dexmedetomidine, an imidazole derivative, is a full adrenoceptor agonist with high selectivity for α_2- compared with α_1-adrenergic receptors (selectivity ratio 1620:1 compared with 220:1 for clonidine) [7]. It causes a dose-dependent decrease in arterial

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blood pressure and heart rate associated with a decrease in serum noradrenaline concentrations [8]. Dexmedetomidine, in a single pre-anesthetic intravenous dose of up to 0.6 μg/kg, has been shown to reduce the requirements for supplementary isoflurane administration during nitrous oxide/oxygen/fentanyl anesthesia and to lessen the hemodynamic reaction to stressful intra-operative events, while causing few side-effects [9]. The purpose of this study was to investigate whether the higher intravenous dose of dexmedetomidine, 2 μg/kg, would eliminate the need for isoflurane supplementation of nitrous oxide/oxygen/fentanyl anesthesia and provide hemodynamic stability during tracheal intubation, emergence and the early postoperative period. Previous studies in healthy volunteers have indicated that this dose is well tolerated [10–12].

Methods

The study was double-blind, randomized and placebo controlled with two groups, dexmedetomidine and placebo. Power analysis before the study indicated that 25 patients in each of the two groups would give an 80% chance of detecting a 30% difference in anesthetic-sparing effect. The study was approved by the Medical Ethical Committee of the hospital and written informed consent was obtained from all patients. Patients with childbearing potential, a known allergy or who weighed more than 100 kg were not studied.

We investigated 50 patients, ASA 1 or 2, aged between 18 and 65 years, who were scheduled for elective minor surgery (general, urological or orthopaedic). All patients were interviewed the evening before and the morning after surgery.

Study procedure and measurements

Systolic blood pressure, diastolic blood pressure and heart rate were measured non-invasively using an automated sphygmomanometer (Datex Cardiocap) and ECG monitor. Peripheral oxygen saturation was measured by pulse oximetry.

On the evening before surgery the arterial blood pressure was measured by the Korotkoff method. The measurements were taken on the same arm throughout the study at the following times: the evening before surgery; on arrival in the anesthetic room; 5 min before and at 1-min intervals during trial medication administration; 1 and 5 min after completion of trial medication administration; just before induction of anesthesia; immediately after induction; 1 min after tracheal intubation; every 3 min during the operative period; every 5 min in the postanesthesia care unit for the first 60 min; thereafter, every 15 min until discharge from the unit.

Blood samples for catecholamine measurements were obtained at the following times: 5 min before trial medication; 1 min before anesthetic induction; 1 min after first skin incision; 30 min into surgery; immediately after arrival in the recovery room; 3 h after arrival in the recovery room. Blood for catecholamine assay was collected into chilled

polypropylene tubes containing potassium-ethylene diamine tetra-acetate; these tubes were stored in ice until centrifuged within 2 h at 0–4°C. The plasma samples were stored at –80 °C until assayed. Samples were transported in carbon dioxide ice to the Department of Pharmacology, University of Turku, Finland, for assay. Concentrations of endogenous catecholamines in venous plasma were determined using high-performance liquid chromatography with coulometric electrochemical detection as described by Scheinin *et al.* [13]. The assay has been shown to be linear at least over a concentration range of 0.25–50 nM for noradrenaline and 0.25–5 nM for adrenaline. The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intra-assay coefficients of variation were 1.55% for noradrenaline and approximately 3% for adrenaline in the relevant concentration ranges.

Anesthesia

Patients were premedicated with atropine 0.5 mg intramuscularly 30 min before scheduled arrival on the anesthetic room. Monitoring was initiated with ECG (lead II), automated noninvasive blood pressure measurement and pulse oximetry (Datex Cardiocap®) and these were recorded continuously (Datex Cardiocap® Recorder). A venous cannula was inserted in the forearm and a glucose/salt solution (3.3% glucose and 0.3% sodium chloride) was commenced at a rate of 6–8 mL · kg^{-1} · h^{-1}. The patient was allowed to rest for 5–10 min after which the first blood samples were obtained. Balanced randomization was carried out using block design (block size 10 patients, five in each group) and random permutations. Patients were allocated randomly to receive, in a double-blind manner, either dexmedetomidine (n = 25) or saline (n = 25). The required amount (2 μg/kg) was transferred to a 20-mL syringe, diluted to 20 mL with physiological saline and given over 5 min through the intravenous cannula. The patients were observed for 15 min, during which period depth of sedation (Ramsey scale [14]) was assessed every 5 min. Following this, induction of anesthesia was initiated.

Fentanyl, 2 μg/kg was given intravenously and the patient was pre-oxygenated for 3 min. Thiopental 3 mg/kg was given intravenously, supplemented, if necessary, with 1 mg/kg aliquots to produce loss of eyelid reflex. After calibration of a Datex Relaxograph®, vecuronium 0.1 mg/kg was given intravenously to provide neuromuscular block. The trachea was intubated and the lungs ventilated with nitrous oxide 67% in oxygen (end-tidal carbon dioxide tension between 3.5 and 4.5 kPa; Datex, Capnomac®). Isoflurane was added, if necessary, and adjusted in steps of 0.25% every 3 min when systolic blood pressure exceeded pre-anesthetic values by 20% or more. When systolic blood pressure decreased below this value, isoflurane was reduced in 0.25% steps every 3 min. End-tidal concentrations of isoflurane were measured continuously using a Datex, Capnomac® monitor. If the heart rate exceeded 100 bpm the patient was given fentanyl in increments of 1 μg/kg intravenously. In addition to the hemodynamic signs of anesthetic depth, we looked for other clinical

signs of 'lightness' such as sweating, lacrimation, swallowing and movement. If necessary, anesthesia was deepened with isoflurane in 0.25% steps until judged adequate. Neuromuscular block was maintained with vecuronium 0.025 mg/kg when the T1 (Relaxograph) exceeded 10%. Isoflurane was discontinued, if possible, 10 min before the end of surgery. Residual neuromuscular block was antagonised with neostigmine 2.5 mg intravenously preceded by atropine 1 mg.

The interval from discontinuation of inhalation of nitrous oxide at the end of surgery to the time when the patient spontaneously opened his/her eyes (the emergence period) was recorded together with the time to perform simple commands (grip hand) and the time to fitness for discharge from the postanesthesia care unit. All patients were monitored in this unit for at least 3 h after surgery. Piritramide 20 mg intramuscularly was given if the patient complained of moderate or severe pain and alizapride 100 mg intravenously was used to treat emetic complications.

The anesthetist assessed the quality of induction and recovery using a visual analogue scale (marking on an ungraded 100-mm-long horizontal line with 0 = extremely poor and 100 = excellent at opposite ends). The following morning all patients evaluated their experience of the period from administration of trial drug until discharge from the unit using a similar scale.

Hypotension (systolic blood pressure < 90 mm Hg) was treated with a rapid infusion of 250 mL of glucose–salt solution, followed by ephedrine 2.5 mg in repeated doses if systolic blood pressure did not increase above 90 mm Hg within 2 min. Bradycardia (heart rate < 45 bpm) was treated with atropine in 0.5 mg intravenously.

Blinding

Because of the sedative and hemodynamic effects seen in the dexmedetomidine group special attention was given to the blinding procedure. An anesthetist not present during administration of trial drug and induction of anesthesia independently assessed the hemodynamic and clinical signs of anesthetic depth in the operating room. In addition, a print-out of all monitored variables was obtained and checked against the clinical record form by an independent observer.

Statistical analysis

The mean expiratory concentration of isoflurane was calculated as the sum of the products of expiratory concentrations and times (area under the curve – AUC) divided by total anesthesia time. Patient characteristics, operation and recovery times, anesthetic requirements and patient and anesthetist's evaluations were analysed using Student's *t*-test; hemodynamic and plasma catecholamine data were analysed using unbalanced two-way analysis of variance for repeated measurements (RM ANOVA). Hemodynamic variability was evaluated by assessing the AUC of systolic blood pressure and heart rate deviations from time-averaged mean. Mann–Whitney testing

was used to analyse the differences between the treatment groups for piritramide and alizapride requirements. Results are presented as mean ± SD unless otherwise stated and $P < 0.05$ was considered statistically significant.

Results

All patients were included in the statistical analysis. The physical characteristics and operation times of the two groups of patients were similar (Table 8-1) with 49 men and one women studied. Patients underwent a variety of surgical procedures (Table 8-2), mainly superficial surgical and minor orthopedic; the distribution of operative procedures was similar in the two groups.

Table 8-1 Patient details and operation times

	Dexmedetomidine ($n = 25$)	Placebo ($n = 25$)
Weight (kg)	76.8 ± 9.3	74.48 ± 10.4
Height (cm)	177.2 ± 7.1	178.2 ± 7.0
Age (years)	42.4 ± 12.7	38.9 ± 14.2
Induction to last suture (min)	68.6 ± 23.4	75.0 ± 26
Incision to last suture (min)	44.0 ± 21.6	48.5 ± 24.3

Values are expressed as mean ± SD.

Table 8-2 Number of patients undergoing the operative procedures shown

	Dexmedetomidine ($n = 25$)	Placebo ($n = 25$)
Superficial surgical	14	14
Minor orthopaedic	2	5
Joint surgery	9	6

Superficial surgical procedures included inguinal and incisional hernia repair, operations for varicose veins, hydrocoele, pilonidal sinus. Minor orthopaedic procedures included removal of exostoses, plates and/or screws, osteotomy of a digit, arthrodesis of the foot. Joint surgery included non-replacement surgery of the shoulder or knee.

Anesthetic requirements

Six out of the 25 patients receiving dexmedetomidine required isoflurane compared with 18 of the 25 patients in the placebo group. The mean intra-operative isoflurane concentration in the dexmedetomidine group was significantly less than in the placebo group (Table 8-3).

More thiopental was required for induction and more fentanyl during operation in the placebo group (Table 8-3). The doses of muscle relaxant required during operation was similar in the two groups (Table 8-3).

Table 8-3 Mean ± SD doses of the drugs shown

	Dexmedetomidine (n = 25)	Placebo (n = 25)	P
Mean intra-operative isoflurane concentration (%)	0.01 ± 0.03	0.1 ± 0.1	$P < 0.001$
Thiopental for induction (mg)	230.6 ± 28	268.0 ± 48.4	$P = 0.002$
Fentanyl during operation (μg)	156.6 ± 23.7	233.4 ± 72.5	$P < 0.001$
Vecuronium (mg)	10.9 ± 2.8	11.9 ± 3.6	$P = 0.3$
Piritramide dose (mg)	5.60 ± 10.83	13.60 ± 12.54	$P = 0.01$
Alizapride dose (mg)	0.00 ± 0.00	32.00 ± 61.03	$P = 0.005$

The mean expiratory concentration of isoflurane was calculated as the sum of the products of expiratory concentrations and times (area under the curve – AUC) divided by total anesthesia time.

Cardiovascular effects

Initial systolic blood pressure was similar in the two groups. Administration of the study drug had no significant effect on systolic or diastolic blood pressure (Figure 8-1). There was a statistically significant difference in initial heart rate (P = 0.003) between the two groups. During drug administration this difference increased (drug*time effect; $P < 0.001$).

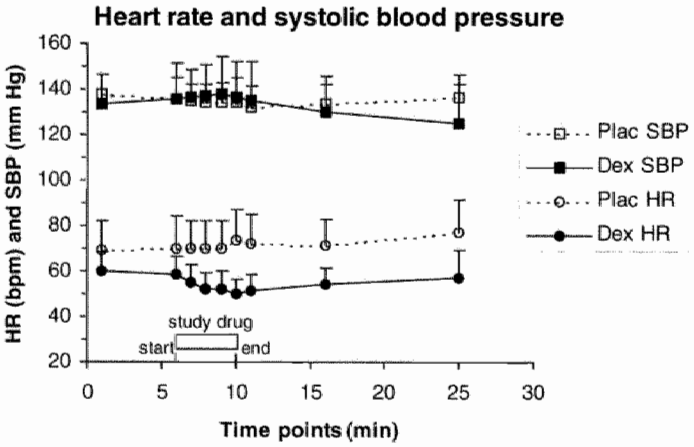

Figure 8-1 Heart rate (HR) and systolic blood pressure (SBP) from 5 min before starting administering the trial drug until 15 min after completion of administration. Dex = dexmedetomidine; Plac = placebo. Values are mean ± SD. There was a significant difference in HR between the two groups during this period ($P < 0.001$).

Laryngoscopy and tracheal intubation resulted in 0 and 31 mm Hg mean increases in systolic blood pressure in the dexmedetomidine and placebo groups, respectively. Increases for diastolic blood pressure were 1 and 26 mm Hg and for heart rate 13 and 29 bpm in the dexmedetomidine and placebo groups, respectively. These differences were significant. The two groups were compared during the first 51 min after tracheal intubation (intra-operative period). The systolic blood pressure, diastolic blood pressure and heart rate were significantly lower in the dexmedetomidine group during this period ($P < 0.001$; drug effect, two-way ANOVA), as were maximum and minimum values for systolic blood pressure and heart rate (Table 8-4).

Table 8-4 Mean ± SD and range minimum and maximum systolic blood pressure (SBP) and heart rate (HR) during and after anaesthesia as indicated

	Dexmedetomidine ($n = 25$)	**Placebo ($n = 25$)**	***P***
(a) From just after induction of anesthesia until end of operation			
Minimal SBP (mm Hg)	97.0 ± 12.1	110.2 ± 12.7	$P < 0.001$
	79 – 120	85 – 133	
Maximal SBP (mm Hg)	138.6 ± 13.9	166.6 ± 18.0	$P < 0.001$
	110 – 168	140 – 201	
Minimal HR (bpm)	48.2 ± 4.5	52.0 ± 6.6	$P = 0.02$
	39 – 58	41 – 66	
Maximal HR (bpm)	78.8 ± 13.2	114.2 ± 15.1	$P < 0.001$
	55 – 105	83 – 150	
(b) Postoperative			
Minimal SBP (mm Hg)	97.3 ± 10.2	122.6 ± 14.9	$P < 0.001$
	71 – 114	84 – 157	
Maximal SBP (mm Hg)	123.7 ± 12.3	150.4 ± 15.1	$P < 0.001$
	106 – 156	117 – 189	
Minimal HR (bpm)	43.3 ± 3.5	55.9 ± 10.1	$P < 0.001$
	33 – 50	45 – 82	
Maximal HR (bpm)	59.2 ± 7.7	83.0 ± 20.2	$P < 0.001$
	48 – 74	55 – 137	

There was a significant difference in heart rate variability between the two groups during the intra-operative period but not in systolic blood pressure variability (Table 8-5).

One minute post-extubation the mean (± SD) systolic blood pressure (mm Hg) was significantly lower in the dexmedetomidine group compared to the placebo group (128 ± 19.0 compared to 153 ± 18.8; $P < 0.001$). There was a similar change in heart rate (bpm) (70 ± 17.8 compared to 87 ± 23.9; $P < 0.001$).

Table 8-5 Variability in systolic blood pressure and heart rate

Variable	Dexmedetomidine (n = 25)	Placebo (n = 25)	P
Systolic blood pressure (mm Hg)	4.8 ± 1.6	6.0 ± 2.7	P = 0.06
Heart rate (bpm)	3.8 ± 1.4	6.9 ± 2.1	P < 0.001

These parameters were calculated by measuring the areas under the curves (AUC) of systolic blood pressure and heart rate deviations from time-averaged means over the intra-operative period. The AUCs were calculated as deviations both above and below the mean. Because of the differences in the duration of surgery the AUCs were divided by the duration of surgery.

Over a 3-h period in the postanesthesia care unit, the mean systolic blood pressure, diastolic blood pressure and heart rate were significantly lower in the dexmedetomidine group (P < 0.001; drug effect, two-way ANOVA) as were the maximum and minimum systolic blood pressure and heart rate (Table 8-4).

Oxygen saturation

Oxygen saturation remained above 95% throughout the monitored period and there was no difference between groups.

Sedative effects

Approximately 5 min after completion of the administration of trial drug in the dexmedetomidine group the patients were deeply sedated (Ramsey level 4–5). Their

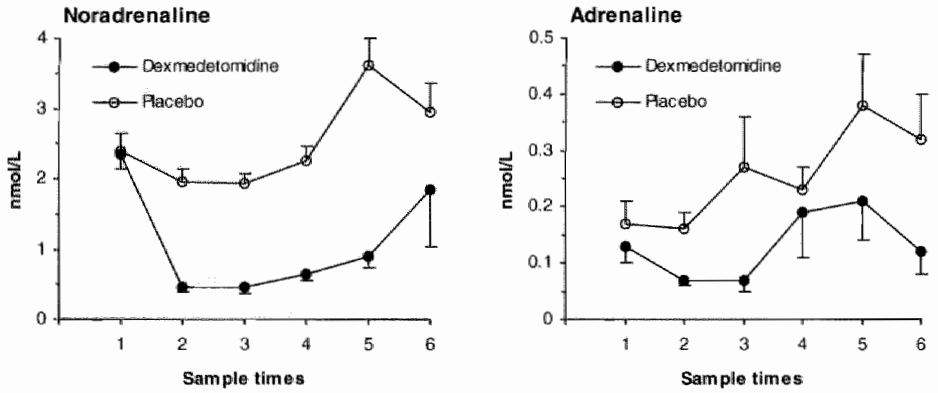

Figure 8-2 Plasma catecholamine concentrations: noradrenaline (left panel) and adrenaline (right panel). Sample times: 1, 5 min before trial drug; 2, 1 min before induction; 3, 1 min after first skin incision; 4, 30 min into surgery; 5, immediately on arrival in postanesthesia care unit (PACU); 6, 3 h after arrival on PACU. Values are mean ± SEM. There was a significant difference between the two groups (adrenaline, P = 0.01; noradrenaline, P < 0.001).

reaction to painful stimuli was reduced, pin-prick producing little or no response. No sedation was seen in the placebo group.

The respiratory rate was unchanged, but three patients (12%) in the dexmedetomidine group developed a partial respiratory obstruction which disappeared if they were roused.

Catecholamines

The plasma noradrenaline concentration was reduced by 75% following dexmedetomidine (Figure 8-2) and the increase seen in the placebo group after anesthesia and surgery did not occur. The plasma adrenaline concentrations followed a similar pattern.

Postoperative recovery

Times to spontaneous eye opening and ability to obey simple commands were similar in the two groups (Table 8-6) and both groups of patients were alert and cooperative on the postanesthesia care unit. However, the time to fitness for discharge was significantly longer in the dexmedetomidine group (Table 8-6) largely due to persistent hypotension (systolic blood pressure < 100 mm Hg) or bradycardia (heart rate < 50 bpm).

Table 8-6 Mean ± SD recovery times

	Dexmedetomidine (n = 25)	**Placebo (n = 25)**	P
Times to awakening (min)	3.5 ± 2.5	3.2 ± 2.9	$P > 0.05$
Obey commands (min)	5.6 ± 3.2	5.1 ± 3.3	$P > 0.05$
Fitness for discharge (min)	133.8 ± 41.3	97.0 ± 37.3	$P = 0.0018$

Times to awakening = time from termination of nitrous oxide until spontaneous eye opening; Obey commands = time from termination of nitrous oxide until ability to grip hand on command; Fitness for discharge = time from arrival on postanesthesia care unit until judged by anesthetist to be fit for discharge to ward.

Patients in the dexmedetomidine group required less analgesia (piritramide) and antiemetic (alizapride) postoperatively than those who were given the placebo treatment (Table 8-3). The visual analogue scale assessment of quality of induction scored by the anesthetist was better for dexmedetomidine than placebo but that for recovery showed no difference (Table 8-7). The patient evaluation visual analogue scale showed no difference between dexmedetomidine and placebo (Table 8-7). No patient complained of intra-operative recall when interviewed on the morning of the first postoperative day.

Table 8-7 Mean ± SD visual analog scores for quality of induction of anesthesia and recovery (anesthetists' assessment) and overall patient assessment

	Dexmedetomidine	Placebo	*P*
Anaestheic induction	86.3 ± 11.8	60.2 ± 15.5	$P < 0.001$
Recovery	80.6 ± 14.2	75.4 ± 15.9	N.S.
Patient assessment	81.9 ± 11.8	74.3 ± 17.8	N.S.

The scale was 100 mm and marked 0 = extremely poor and 100 = excellent at opposite ends.

Side-effects

No allergic phenomena were observed. Following administration of trial drug and during anesthesia ephedrine was required to treat hypotension in five patients in the dexmedetomidine group compared with none in the placebo group; atropine was required to treat bradycardia in six patients in the dexmedetomidine group compared with two in the placebo group. When given shortly after administration of dexmedetomidine, atropine 0.5 mg intravenously increased heart rate but also caused systolic and especially diastolic hypertension which lasted for several minutes. This could be prevented by titrating atropine in 0.05–0.1 mg aliquots until the desired effect was obtained.

In the postanesthesia care unit, bradycardia (heart rate < 45 bpm) occurred in 14 patients in the dexmedetomidine group compared with none in the placebo group. One dexmedetomidine-treated patient developed sudden reductions in heart rate (33 bpm) and systolic blood pressure (71 mm Hg) 2 h after arrival in the unit. This was accompanied by symptoms of feeling unwell and dizziness. Atropine 0.5 mg and 250 mL glucose–salt solution (3.3% glucose and 0.3% sodium chloride) were given with immediate improvement. Two minutes later heart rate was 66 bpm and blood pressure 119/76 mm Hg. Further recovery was uneventful.

Discussion

The most likely site of the hypnotic/anesthetic action of dexmedetomidine is a postsynaptic α_2-adrenoceptor [15] located in the locus coeruleus [16] which involves an inhibitory pertussis-toxin-sensitive G protein and increased conductance through a potassium channel [17]. In dogs treated with dexmedetomidine, the MAC for halothane was decreased by > 90% following 10 μg/kg intravenously [18], and in rats treated with dexmedetomidine 100 μg/kg intraperitoneally, halothane could be discontinued for up to 30 min without eliciting a purposeful response to tail-clamping [19].

Various studies in humans have demonstrated the anesthetic-sparing effects of dexmedetomidine for both thiopental [20] and isoflurane [9,21]. The relatively high intravenous dose of 2 μg/kg dexmedetomidine used here has not previously been

investigated in a clinical anesthetic study. In our study we achieved a reduction in isoflurane requirements of 90%, similar to that found by Aho *et al.* using a two-stage infusion technique in patients undergoing cholecystectomy [21], but it was not possible to avoid the use of isoflurane entirely, six patients requiring it at some stage. The decrease in anesthetic requirements does not lead to more rapid recovery of consciousness, since there was no difference in the recovery times measured.

A biphasic effect on hemodynamics is seen after intravenously dexmedetomidine [12]; an immediate increase in systemic arterial pressure (mediated by stimulation of peripheral α_2-adrenoceptors [22]) followed by a longer lasting reduction in pressure caused by stimulation of α_2-adrenoceptors in the central nervous system. The initial pressor effect is influenced by the rate of intravenous infusion. In healthy volunteers, a maximum increase in systolic blood pressure of 24 ± 10 mm Hg occurred 3 min after dexmedetomidine 2 μg/kg given over 2 min intravenously [12]. By infusing dexmedetomidine over 5 min we saw no increase in systolic blood pressure (Figure 8-1).

Increases in systolic blood pressure and heart rate have been shown to be causally related to peri-operative ischaemia in patients with cardiovascular disease [23]. Laryngoscopy and tracheal intubation as well as emergence from anesthesia and extubation are known to be particularly dangerous periods for patients with ischaemic heart disease. The almost complete suppression of the pressor response to intubation seen in the dexmedetomidine patients together with the lesser increase in heart rate led to a lower rate pressure product. Moreover, the decreased intra-operative heart rate variability despite a reduction in anesthetic requirement may also be beneficial in these patients.

The continuation of a stabilising effect on blood pressure and heart rate throughout the recovery period may be important in patients with coronary artery disease [24].

All patients were sedated (Ramsey 4–5) following dexmedetomidine 2 μg/kg intravenously. This sedation is associated with a diminished response to painful stimuli. Unfortunately, the partial respiratory obstruction seen in a number of patients means that patients cannot be left unattended following intravenous dexmedetomidine in this dose. Irregular breathing and short episodes of apnoea have been described immediately following an intravenous infusion of dexmedetomidine 2 μg/kg in human volunteers [11]. Clonidine has also been associated with an obstructive pattern of respiration, probably due to the sedative effect, and requiring treatment with oxygen [25].

It is known that α_2-adrenergic agonists diminish salivary flow [26] and reduce gastrointestinal motility [27]. This study suggests that dexmedetomidine reduces postoperative nausea and vomiting, although larger studies will be necessary to confirm this.

α_2-Adrenergic agonists have been shown to produce analgesia by action at the α_2-adrenoceptor independent of opioid receptors [28] and their analgesic effects have

been demonstrated in animals [29,30] and in man [31]. The analgesia produced by α_2-agonists is of interest as it has been shown not to be associated with respiratory depression [32,33]. In this study the reduction in postoperative analgesic requirements was not accompanied by a reduction in oxygen saturation.

Dexmedetomidine, like other α_2-adrenergic agonists, exerts sympatholytic effects by activating inhibitory α_2-receptors both in the central nervous system and on peripheral sympathetic nerve endings, resulting in inhibition of noradrenaline release [34]. The inhibition of sympathetic transmitter release can be measured in humans as a decline in the concentration of noradrenaline in plasma. [35]. In our study, the plasma noradrenaline concentration was markedly decreased following dexmedetomidine while the increase in plasma noradrenaline and adrenaline concentrations seen in the placebo group after anesthesia and surgery were attenuated in the dexmedetomidine group. The prevention of the catecholamine reaction to stress by dexmedetomidine may be of clinical importance, since there is a clear relationship between surgical events known to produce intense sympathetic stimulation and perioperative myocardial infarction [23].

Our study has demonstrated that a single pre-induction intravenous dose of dexmedetomidine 2 μg/kg increased hemodynamic stability intra-operatively, during emergence and in the early postoperative period. However, there was a higher incidence of bradycardia and hypotension, as has been described following intramuscular dexmedetomidine [36,37]. In the future dexmedetomidine will probably be administered by continuous infusion in order to reduce the incidence of hemodynamic side-effects [21].

It is important to improve hemodynamic stability in the postoperative period when the highest incidence of cardiovascular complications occurs, especially in high-risk patients [24]. Future research should concentrate on increasing hemodynamic stability intra-operatively, on emergence and in the postoperative period by means of a continuous infusion of dexmedetomidine aiming to achieve a constant plasma concentration [38]. Preliminary results in small patient groups suggest that a plasma dexmedetomidine concentration of 4.5 ng/mL results in a low incidence of tachycardia in the postoperative period in patients undergoing vascular surgery [39]. Larger studies in high-risk cardiovascular patients will be required to confirm these findings.

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References

1 Aho M, Erkola O, Korttila K. Alpha2-adrenergic agonists in anesthesia. *Current Opinion in Anaesthesiology* 1992; **5**: 481–7.

2 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605.

3 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.

4 Ghignone M, Quintin L, Duke P, Kehler C, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.

5 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

6 Engelman E, Lipszyc M, Gilbart E, *et al.* Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–87.

7 Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine–a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; **13**: 635–51.

8 Kallio A, Scheinin M, Koulu M, *et al.* Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. *Clin Pharmacol Ther* 1989; **46**: 33–42.

9 Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; **74**: 997–1002.

10 Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; **78**: 813–20.

11 Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992; **77**: 1125–33.

12 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42.

13 Scheinin M, Koulu M, Laurikainen E, Allonen H. Hypokalaemia and other non-bronchial effects of inhaled fenoterol and salbutamol: A placebo-controlled dose-response study in human volunteers. *Br J Clin Pharmacol* 1987; **24**: 645–53.

14 Ramsey MAE, Savage TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *British Medical Journal* 1974; **2**: 656–9.

15 Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic–anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology* 1989; **71**: 75–9.

16 Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats [see comments]. *Anesthesiology* 1992; **76**: 948–52.

17 Doze VA, Chen BX, Tinklenberg JA, Segal IS, Maze M. Pertussis toxin and 4-aminopyridine differentially affect the hypnotic–anesthetic action of dexmedetomidine and pentobarbital. *Anesthesiology* 1990; **73**: 304–7.

18 Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha 2-adrenergic agonist, in halothane-anesthetized dogs. *Anesth Analg* 1988; **67**: 611–5.

19 Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. *Anesthesiology* 1988; **69**: 818–23.

20 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5.

21 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992; **75**: 940–6.

22 Nichols A, Hieble J, Ruffolo R. The pharmacology of peripheral alpha 1- and alpha 2-adrenoceptors. *Rev Clin Basic Pharm* 1988; **7**: 129–205.

23 Slogoff S. Perioperative ischemia. *Semin Anesth* 1990; **9**: 1–7.

24 Mangano D, Browner W, Hollenberg M, Li J, Tateo I. SPI Research Group. Peri-operative myocardial ischemia in patients undergoing non-cardiac surgery. I: Incidence and severity during the 4 day peri-operative period. *J Am Coll Cardiol* 1991; **7**: 843–50.

25 Benhamou D, Veillette Y, Narchi P, Ecoffey C. Ventilatory effects of premedication with clonidine. *Anesth Analg* 1991; **73**: 799–803.

26 Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha 2-adrenoceptor agonist effects by atipamezole in human volunteers. *Br J Clin Pharmacol* 1991; **31**: 160–5.

27 Wikberg J. Localization of adrenergic receptors in guinea pig ileum and rabbit jejunum to cholinergic neurons and to smooth muscle cells. *Acta Physiol Scand* 1977; **99**: 190–207.

28 Spaulding TC, Fielding S, Venafro JJ, Lal H. Antinocioceptive activity of clonidine and its potentiation of morphine analgesia. *Eur J Pharmacol* 1979; **58**: 19–25.

29 Puke MJ, Wiesenfeld HZ. The differential effects of morphine and the alpha 2-adrenoceptor agonists clonidine and dexmedetomidine on the prevention and treatment of experimental neuropathic pain. *Anesth Analg* 1993; **77**: 104–9.

30 Ylisela E, Vainio O. Effects of medetomidine on the experimental auricular pain in dogs. *Acta Vet Scand Suppl* 1989; **85**: 187–91.

31 Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Korttila KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991; **73**: 112–8.

32 Furst SR, Weinger MB. Dexmedetomidine, a selective alpha 2-agonist, does not potentiate the cardiorespiratory depression of alfentanil in the rat. *Anesthesiology* 1990; **72**: 882–8.

33 Bailey PL, Sperry RJ, Johnson GK, *et al*. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology* 1991; **74**: 43–8.

34 Langer S. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 1981; **32**: 337–62.

35 Scheinin M, Kallio A, Koulu M, Viikari J, Scheinin H. Sedative and cardiovascular effects of medetomidine, a novel selective alpha 2-adrenoceptor agonist, in healthy volunteers. *Br J Clin Pharmacol* 1987; **24**: 443–51.

36 Levanen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology* 1995; **82**: 1117–25.

37 Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. *Anesth Analg* 1992; **75**: 932–9.

38 Dyck JB, Maze M, Haack C, Azarnoff DL, Vuorilehto L, Shafer SL. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; **78**: 821–8.

39 Talke P, Li J, Jain U, *et al*. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology* 1995; **82**: 620–33.

CHAPTER 9

General discussion

9.1 Cardiovascular effects

The first major aim of this study was to investigate whether the initial peripheral α_2-adrenergic vasoconstriction could be a concern for the use of selective α_2-adrenergic agonists like dexmedetomidine. The present studies demonstrated a reduction in heart rate and redistribution of coronary blood flow which are potentially beneficial to the more vulnerable endocardium, together with maintainance of the balance of myocardial oxygen supply and demand (Chapters 5 and 7). Reduction in cardiac output was associated with a relative sparing of nutrient perfusion of vital organs (Chapter 6).

9.2 Vascular effects

We found that the cardiovascular effects of dexmedetomidine and clonidine were qualitatively similar, but that dexmedetomidine is 3 to 10 times more potent than clonidine in causing bradycardic and vasoconstrictive effects. The systemic and coronary vasoconstriction, but not the bradycardic effect, are shorter lived after dexmedetomidine than after clonidine. At high doses (10 and 30 μg/kg) clonidine has persistent negative inotropic and coronary vasoconstrictive effects not shown by high dose dexmedetomidine (Chapter 4).

The immediate reaction after a 2-min intravenous dose of dexmedetomidine is an increase in arterial blood pressure and systemic vascular resistance and this is seen in dogs (Chapter 5), goats (Chapter 7) and in humans [1]. This blood pressure effect is dose-dependent and is significant with doses $\geq$ 0.3 μg/kg dexmedetomidine in the dog (Figure 4-1), $\geq$ 1 μg/kg in the goat (Figure 7-1), and $\geq$ 1 μg/kg in humans [1]. In the clinical study using 2 μg/kg (Chapter 8), we were able to avoid the pressor effect by giving dexmedetomidine over 5 min. More recently, studies of α_2-adrenergic agonists have used a continuous infusion to achieve a constant plasma level [2–4].

Our studies also suggest a species difference in the initial vasoconstrictor effect, dogs showing a more persistent increase in blood pressure and systemic vascular resistance

than goats (Figures 4-1, 4-2, 7-1 and 7-2). In this, goats appear to behave less like dogs and more like humans, where the most commonly seen response is a short-lived hypertension followed within minutes by a reduction in blood pressure [5].

9.3 Coronary vasoconstriction

We demonstrated that in dogs, especially under chloralose/urethane anesthesia, dexmedetomidine reduces myocardial blood flow. At doses ≤ 3 μg/kg, this is primarily due to a decrease in myocardial oxygen requirement. Moderate adrenergic coronary vasoconstriction (as shown by increased oxygen extraction) occurs after 10 μg/kg (Table 5-3). Therefore, the oxygen sparing effect occurs at a lower dose than vasoconstriction. Increased oxygen extraction occurred with unchanged lactate production, an indication that aerobic metabolism was maintained.

In the goat we found unchanged oxygen extraction even after 10 μg/kg dexmedetomidine (Figure 7-3). Thus goats may possess a lesser tendency for coronary vasoconstriction at high doses of dexmedetomidine. Since the peripheral vasoconstrictor (pressor) effect was less in goats than in dogs and more like that in humans (see above), it is probable that α_2-coronary vasoconstriction is not as severe in humans as in dogs. The latter species has most commonly been used for experiments demonstrating increased coronary vasoconstriction after α_2-adrenergic agonists [6]. Indolfi has shown in humans with normal coronary arteries that coronary artery blood velocity decreased by a maximum of 28% after intracoronary administration of an α_2-adrenergic agonist [7], supporting the idea that the coronary vasoconstrictive effect of α_2-agonists is moderate in humans. It is important to note that at the dose of dexmedetomidine used till now in clinical anesthesia (between 0.5 and 2 μg/kg), the myocardial energy sparing effect prevails even in dogs and vasoconstrictive effects are negligible.

The data from our study appear to contradict that from other studies in dogs. Flacke *et al.* suggested that the coronary vasoconstriction seen after dexmedetomidine might lead to myocardial ischemia [8]. However, the present studies showed that reduction in coronary blood flow and increase in coronary vascular resistance occur in parallel with reduced myocardial energy demands. Heusch's group showed that cardiac sympathetic nerve stimulation [9] and exercise [10], both combined with α_1-receptor blockade, elicited myocardial ischemia in dogs with coronary artery stenosis. However, their experimental conditions are quite different from those in our studies, where the central sympatholytic effects of the α_2-receptor agonist were more important.

Therefore, it may be concluded that with slow intravenous administration α_2-adrenergic agonists have no untoward myocardial effects. Furthermore, the finding that dexmedetomidine increases endocardial/epicardial blood flow ratio in dogs with normal coronary perfusion indicates support for the perfusion of the myocardial layer which is most vulnerable to a reduction in coronary blood flow.

9.4 Contractility

In both dogs and goats we observed an increase in left ventricular end-diastolic pressure (LVEDP) immediately following infusion of dexmedetomidine (Tables 4-1 and 7-1), but this was short-lived, LVEDP returning to baseline within 15 min. $LVdP/dt_{max}$ was decreased 15 minutes following dexmedetomidine in dogs (Table 5-1) and in goats (Table 7-1). This indicates a reduction in myocardial contractility, which may be due to one of a number of possible mechanisms; a direct effect on the myocardium is unlikely, since dexmedetomidine has no direct effect upon myocardial cells [11,12]; a reduction in contractility due to myocardial ischemia is unlikely as we have shown that myocardial oxygen balance is maintained in dogs and goats (Chapters 5 and 7) and complete reversal of the peripheral and coronary vasoconstriction with ATP only partially reversed the reduction in cardiac function induced by dexmedetomidine [13]. Therefore, the reduction in myocardial contractility is most likely due to dexmedetomidine's sympatholytic effect as evidenced by reduced plasma catecholamines (Chapter 8). The reduction in myocardial contractility and heart rate contributes to the decrease in myocardial oxygen consumption.

9.5 Nutrient organ flow

In most species, except for the pig [14], α_2-adrenergic agonists cause a reduction in cardiac output. We saw a reduction of 50% in cardiac output after dexmedetomidine 10 μg/kg in both dogs (Figure 4-2) and goats (Table 7-1), and after clonidine 30 μg/kg in dogs (Figure 4-2). In human volunteers, dexmedetomidine 2 μg/kg intravenously (the dose used in our clinical study) decreased cardiac output by 17% [1]. In the dog, dexmedetomidine decreased blood flow to most organs, but the largest decrease (70%– 90%) occurred in skin and in flow through arterio-venous anastomoses. Renal blood flow decreased by 30%, cerebral blood flow only when baseline blood flow was high (in the fentanyl/halothane group), and left ventricular blood flow only in the chloralose/urethane group, where the largest decrease in hemodynamic variables occurred (Chapter 6). Overall adequacy of oxygen supply to the body was indicated by unchanged or even lowered arterial plasma lactate concentrations, even at the highest (10 μg/kg) dose of dexmedetomidine (Table 5-3). In our clinical study we observed a marked pallor of the skin of patients immediately following the intravenous infusion of dexmedetomidine, strongly suggesting that marked cutaneous vasoconstriction occurred in man, which has earlier been shown for clonidine [15]. The adequacy of myocardial oxygen supply has been discussed above. Other investigators have shown that cerebral metabolic rate for oxygen does not decrease when cerebral blood flow is reduced following dexmedetomidine in dogs receiving halothane or isoflurane anesthesia [16,17]. Therefore, the reduction in cardiac output caused by dexmedetomidine appears to be due to a combination of redistribution of flow away from less vital organs and decreased energy demands of the vital organs.

9.6 Advantages as an anesthetic adjuvant in humans

The second main aim of this thesis was to investigate the effects of dexmedetomidine in humans. In a study of healthy patients undergoing minor surgery, we showed that a single intravenous dose of dexmedetomidine 2 μg/kg given prior to anesthesia resulted in a reduction in anesthetic requirements and improved peri-operative hemodynamic stability accompanied by lower plasma catecholamine levels. Post-operatively, less analgesic and anti-emetic medication was required. Dexmedetomidine was well tolerated in this group of healthy patients.

9.7 Anesthetic reduction

Some of the initial studies of α_2-adrenergic agonists in anesthesia were carried out using intravenous clonidine. These studies were performed mainly in Europe because in the U.S.A. only the use of an oral preparation was officially approved by the FDA. With the development of the more selective α_2-adrenergic agonist dexmedetomidine, research into the anesthetic sparing and hemodynamic stabilizing effects of α_2-adrenergic agonists continued using this agent administered by a variety of routes, oral, intramuscular and intravenous. Our study (Chapter 8) and that of Aho *et al.* have shown that dexmedetomidine is capable of greater reductions in anesthetic requirement of up to 90% [18] compared to 50% for clonidine [19,20].

Both these dexmedetomidine studies can be criticised on the grounds that hemodynamic criteria (systolic blood pressure and heart rate) were used as a measure of anesthetic depth. There is always a danger of awareness when using anesthetic agents possessing hemodynamic effects in addition to their anesthetic properties. However, for clonidine it has been shown that similar reductions in anesthetic requirements occurred in experiments using either hemodynamic criteria [21] or continuous electro-encephalogram (EEG) [19,20] as indicator of anesthetic depth. In our clinical study no patient in either group reported awareness when interviewed on the day following surgery (Chapter 8).

9.8 Analgesia and anti-emetic effect

Our patients showed a decrease in postoperative analgetic requirements. A reduction in postoperative pain after α_2-adrenergic agonists has been demonstrated for dexmedetomidine [22] and for clonidine [23]. In addition, we demonstrated a reduction in the incidence of nausea and vomiting in the dexmedetomidine group. Clonidine has also been shown to be effective in reducing postoperative vomiting when given prophylactically in children [24]. Since nausea and vomiting is common in the post-operative period, and is responsible for much patient discomfort, such an anti-emetic effect is of considerable benefit to patient comfort.

9.9 Sympatholysis

Whereas the sympathetic nervous system is important in helping to mobilize energy stores and in optimizing the "fight and flight" response, such reactions are not useful in humans undergoing anesthesia and surgery. Increases in plasma levels of cortisol, glucagon and catecholamines and other hormones lead to major metabolic changes which are often harmful to the surgical patient and anesthesiologists have recently shown increased interest in modifying these responses [25]. Epidural anesthesia can markedly suppress the increase in many of the stress hormones during lower abdominal surgery [26], but are less effective for upper abdominal surgery [27]. Inhalational agents do not seem to suppress the response to stress [28,29]. High doses of opioids, *e.g.* 4 mg/kg of morphine and 100 μg/kg of fentanyl, markedly reduce the hormonal response to surgery [30], but are only suitable for operations where post-operative ventilation is a standard part of the anesthetic technique (*e.g.* cardiac surgery).

α_2-Adrenergic receptor stimulation seems to provide ideal control during anesthesia and surgery, limiting the increases seen in catecholamines and vasopressin [31], cortisol [32], and other hormones. We have shown in our clinical study in healthy patients that a single pre-induction dose of dexmedetomidine depresses the normal post-operative increase in circulating catecholamines (Figure 8-2) and stabilises peri-operative blood pressure and heart rate (Table 8-4). Stress may also be diminished post-operatively by improved analgesia with a reduced tendency for nausea and vomiting.

9.10 Effects on ischemic myocardium

Since we completed the experiments described here, further studies have been performed in our laboratory specifically aimed at potentially beneficial effects of α_2-adrenergic agonists on the ischemic myocardium. It was found that the α_2-adrenergic agonists dexmedetomidine and mivazerol improved endocardial/epicardial blood flow ratio and reduced myocardial oxygen deficit in dogs with coronary artery stenosis [33,34]. A large multi-center study has shown that a continuous intravenous infusion of mivazerol reduced the incidence of myocardial ischemia in the perioperative period in patients undergoing peripheral vascular surgery [2]. Thus, in addition to the favourable effects of the newer selective α_2-adrenergic agonists as anesthetic adjuvants demonstrated in patients with a normal cardiovascular system (this thesis), they may also prove to be beneficial in patients with coronary vascular disease.

9.11 Conclusions

We can conclude the following:

1. Dexmedetomidine is 3–10 times more potent for hemodynamic effects than clonidine; slow infusion is more important for a selective α_2-adrenergic agonist like dexmedetomidine than for clonidine (Chapter 4).
2. Dexmedetomidine reduces myocardial oxygen requirements in parallel with oxygen consumption (Chapter 5).
3. In dogs with normal coronary arteries, dexmedetomidine increases the endocardial/epicardial blood flow ratio (Chapter 5).
4. In goats, dexmedetomidine caused less vasoconstriction than in dogs while the systemic hemodynamic effects were similar to those seen in humans. This suggests that humans are less susceptible to α_2-adrenergic coronary vasoconstriction than dogs (Chapters 5 and 7).
5. Dexmedetomidine redistributes cardiac output, with preferential reduction in flow to the skin as well as through arterio-venous anastomoses, while flow to vital organs is relatively better preserved (Chapter 6).
6. Dexmedetomidine premedication in healthy patients causes sedation and a reduction in anesthetic requirements and improves hemodynamic stability while reducing analgesic and anti-emetic requirements post-operatively. Although hypotension and bradycardia occur more commonly after dexmedetomidine, no harmful effects were seen (Chapter 8).

References

1 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42.

2 McSpi-Europe RG. Perioperative sympatholysis: Beneficial effects of the α_2-adrenergic agonist mivazerol on hemodynamic stability and myocardial ischemia. *Anesthesiology* 1997; **86**: 346–63.

3 Talke P, Li J, Jain U, *et al.* Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology* 1995; **82**: 620–33.

4 Jalonen J, Hynynen M, Kuitunen A, *et al.* Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology* 1997; **86**: 331–45.

5 Bloor BC, Schmeling WT. Cardiovascular effects of α_2-adrenoceptors. *Anaesth Pharm Rev* 1993; **1**: 246–62.

6 Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation* 1990; **81**: 1–13.

7 Indolfi C, Piscioni F, Villari B, *et al.* Role of alpha$_2$-adrenoceptors in normal and atherosclerotic human coronary circulation. *Circulation* 1992; **86**: 1116–24.

8 Flacke WE, Flacke JW, Bloor BC, McIntee DF, Sagan M. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *J Cardiothorac Vasc Anesth* 1993; **7**: 41–9.

9 Heusch G, Deussen A. The effects of cardiac sympathetic nerve stimulation on the perfusion of stenotic coronary arteries in the dog. *Circ Res* 1983; **53**: 8–15.

10 Seitelberger R, Guth B, Heusch G, Lee J, Katayama K, Ross JJ. Intracoronary alpha 2-adrenergic receptor blockade attenuates ischemia in conscious dogs during exercise. *Circ Res* 1988; **62**: 436–42.

11 Flacke WE, Flacke JW, Blow KD, McIntee DF, Bloor BC. Effect of dexmedetomidine, an alpha 2-adrenergic agonist, in the isolated heart. *J Cardiothorac Vasc Anesth* 1992; **6**: 418–23.

12 Housmans PR. Effects of dexmedetomidine on contractility, relaxation, and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990; **73**: 919–22.

13 Roekaerts P. Alpha$_2$-adrenergic receptor agonists in myocardial ischemia, University of Maastricht, 1997.

14 Jalonen J, Halkola L, Kuttila K, *et al.* Effects of dexmedetomidine on coronary hemodynamics and myocardial oxygen balance. *J Cardiothorac Vasc Anesth* 1995; **9**: 519–24.

15 Coffman JD, Cohen RA. Role of alpha-adrenoceptor subtypes mediating sympathetic vasoconstriction in human digits. *Eur J Clin Invest* 1988; **18**: 309–13.

16 Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesth Analg* 1990; **70**: 624–30.

17 Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs [see comments]. *Anesth Analg* 1990; **71**: 125–9.

18 Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992; **75**: 940–6.

19 Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.

20 Ghignone M, Quintin L, Duke P, Kehler C, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.

21 Flacke J, Bloor B, Flacke W, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9.

22 Aho MS, Erkola OA, Scheinin H, Lehtinen AM, Korttila KT. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991; **73**: 112–8.

23 Mikawa K, Nishina K, Maekawa N, Obara H. Oral clonidine premedication reduces postoperative pain in children. *Anesth Analg* 1996; **82**: 225–30.

24 Mikawa K, Nishina K, Maekawa N, Asano M, Obara H. Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42**: 977–81.

25 Biebuyck J. The metabolic response to stress: An overview and update. *Anesthesiology* 1990; **73**: 308–27.

26 Engquist A, Fog-Moller F, Christiansen C, Thode J, Anderson T, Nistrup-Madsen S. Influence of epidural analgesia on the catecholamine and cyclic AMP response to surgery. *Acta Anesthiol Scand* 1980; **24**: 17–21.

27 Asoh T, Tsuji H, Shirasaka C, Takeuchi Y. Effect of epidural analgesia on metabolic response to major abdominal surgery. *Acta Anesthesiol Scand* 1983; **27**: 233–7.

28 Oyama T, Taniguchi K, Ishihara H, *et al.* Effects of enflurane anaesthesia and surgery on endocrine function in man. *Br J Anaesth* 1979; **51**: 141–8.

29 Lacoumenta S, Paterson J, Burrin J, Causon R, Brown M, Hall G. Effects of two differing halothane concentrations on the metabolic and endocrine responses to surgery. *Br J Anaesth* 1986; **58**: 844–50.

30 Walsh E, Paterson J, O'Riorden J, Hall G. Effect of high dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. *Br J Anaesth* 1981; **53**: 1155–65.

31 Quintin L, Roudot F, Roux C, *et al.* Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *Br J Anaesth* 1991; **66**: 108–15.
32 Kallio A, Koulu M, Scheinin H, Viikari J, Scheinin M. Acute effects of medetomidine, a selective alpha 2-adrenoceptor agonist, on anterior pituitary hormone and cortisol secretion in man. *Acta Endocrinol Copenh* 1988; **119**: 11–5.
33 Roekaerts PM, Prinzen FW, Willigers HM, De LS. The effects of alpha 2-adrenergic stimulation with mivazerol on myocardial blood flow and function during coronary artery stenosis in anesthetized dogs. *Anesth Analg* 1996; **82**: 702–11.
34 Roekaerts P, Prinzen F, de Lange S. Beneficial effects of dexmedetomidine on ischaemic myocardium in anaesthetized dogs. *Br J Anaesth* 1996; **77**: 427–9.

Summary

Improvements in anesthesia and perioperative patient care have allowed patients to undergo surgery with a minimum of discomfort and complications. Although anesthesia can, during less stressful surgery, protect patients against the harmful effects of noxious stimuli, it is not always possible to provide optimal protection throughout all types of surgery without recourse to invasive techniques (like epidural analgesia) or large doses of anesthetic agents which may cause hemodynamic instability and prolong recovery. In order to provide stable anesthesia without recourse to high doses of anesthetics, other pharmacological agents which are not themselves anesthetics may be applied as anesthetic adjuvants. Recently, α_2-adrenergic receptor agonists have been advocated as such anesthetic adjuvants since they provide sedation, and reduce anxiety, nausea and pain (Chapter 3). These effects are more apparent following the recently developed agents with a greater selectivity for the α_2-receptors than the "classic" α_2-adrenergic agonist clonidine.

The anesthetic effects of dexmedetomidine and other α_2-adrenergic agonists are due to stimulation of α_2-adrenergic receptors in centers such as the locus coeruleus in the brain.

α_2-Receptors are found also in the walls of blood vessels where they cause vasoconstriction. Some animal studies raised concerns about the potential vasoconstrictive effects of α_2-agonists on α_2-receptors in peripheral and coronary arteries. Therefore, before exploring the use of dexmedetomidine in clinical anesthesia, we investigated its cardiovascular effects on the normal cardiovascular system in detail. Since more invasive studies on coronary blood flow and oxygen requirements of the heart can be performed in experimental animals, we studied the effects of dexmedetomidine on the cardiovascular system in anesthetized dogs and goats. Finally, we carried out a clinical study in humans to better evaluate the benefits and cardiovascular effects of a pre-anesthetic dose of dexmedetomidine on healthy patients undergoing minor surgery.

In Chapter 4, we compared the hemodynamic effects of clonidine with dexmedetomidine in dogs using a range of doses. Both agents caused a transient increase in arterial blood pressure and systemic vascular resistance and a longer-lasting decrease in heart rate and cardiac output, but dexmedetomidine was 3–10 times more potent than clonidine for the pressor effects. Within 15 min the pressor effect recovered considerably for doses $\leq$ 3 μg/kg of dexmedetomidine and clonidine. High dose

clonidine (10 and 30 μg/kg) induced prolonged coronary vasoconstriction and reduction in myocardial contractility. These results indicate that slow intravenous administration is more important for the potent and selective α_2-adrenergic agonist dexmedetomidine than for clonidine, and that dexmedetomidine lacks the ontoward α_1-adrenergic effects, occurring at high doses of clonidine.

In Chapters 5 and 6 we describe the hemodynamic effects of dexmedetomidine in dogs anesthetized with either chloralose/urethane or fentanyl/halothane. The rapid, transient increase in blood pressure, systemic vascular resistance and left ventricular end-diastolic pressure, and longer-lasting reduction in cardiac output and heart rate was similar in both dog groups. Fifteen minutes later the effect was dependent on anesthetic technique. In chloralose/urethane anesthetized dogs, blood pressure decreased, whereas in fentanyl/halothane anesthetized dogs blood pressure remained elevated. Thus, anesthetic technique influences the cardiovascular effects of dexmedetomidine in dogs. Since sympathetic tone is known to be greater in dogs anesthetized with chloralose/urethane it is likely that the stabilizing effect of dexmedetomidine on heart rate and blood pressure is greater in situations where the initial sympathetic tone is high.

This stabilizing effect in chloralose/urethane anesthetized dogs was also accompanied by decreased myocardial energy requirement, while myocardial oxygen supply decreased in parallel with demand. Myocardial oxygen extraction increased only after the highest dose of 10 μg/kg dexmedetomidine, but even at this dose the heart continued to extract lactate, indicating the absence of global myocardial ischemia. These data indicate that for dexmedetomidine $\leq$ 3 μg/kg, the reduction in myocardial blood flow is functional; by metabolic vasoregulation rather than adrenergic vasoconstriction. Although total myocardial blood flow is reduced after dexmedetomidine, endocardial/epicardial blood flow ratio is increased, safeguarding the layer most vulnerable to ischemia (Chapter 5).

In Chapter 6, a study of the distribution of cardiac output using radioactive microspheres, we show that the reduction in cardiac output following dexmedetomidine is not the result of an equal reduction of blood flow to all organs. Blood flow to the vital organs (heart, brain, kidneys) is spared and greater reductions occur in the blood flow to less vital organs such as the skin, intestine and spleen and through arterio-venous anastomoses.

After studying the cardiovascular effects of dexmedetomidine in the dog, a species prone to α-adrenergic vasoconstriction, we investigated the goat. We found that the pressor effect of dexmedetomidine in goats was shorter than in dogs, and therefore more like that seen in humans. In goats, dexmedetomidine 10 μg/kg reduced myocardial oxygen extraction (Chapter 7), whereas in the dog this dose increased it (Chapter 5). This indicates that the balance of myocardial oxygen supply and demand is maintained up to a higher dose of dexmedetomidine in goats. If similarity in pressor

response is indicative of the coronary vasoconstrictive effect in goats and humans, humans may be less prone to coronary vasoconstriction following dexmedetomidine.

In the clinical study during minor surgery in healthy adults, we showed that a single intravenous dose of 2 μg/kg dexmedetomidine given over 5 min prior to anesthetic induction reduced the requirements for isoflurane by 90%, for thiopental by 14% and for fentanyl by 33%. Plasma catecholamine levels were lower in the dexmedetomidine patients, indicating a sympatholytic effect. Dexmedetomidine reduced the hemodynamic response to intubation and emergence from anesthesia and increased hemodynamic stability in the peri-operative period. Also, there was a reduced requirement for post-operative analgetic and anti-emetic medication. While the incidence of peri-operative bradycardia was high in these patients, this did not produce adverse hemodynamic effects (Chapter 8).

Therefore, we have demonstrated that the hemodynamic effects of dexmedetomidine do not represent a contraindication to its use during anesthesia. On the contrary, the central sympatholysis together with the many other beneficial effects demonstrated in this thesis suggest that dexmedetomidine is a an excellent agent for use as an anesthetic adjuvant in healthy patients.

Samenvatting

Verbeteringen in anesthesie en peri-operatieve patiëntenzorg hebben ertoe geleid dat patiënten kunnen worden geopereerd met een minimum aan ongemak en complicaties. In de anesthesiologie wordt ook steeds meer ingezien dat anesthesie patiënten kan beschermen tegen de nadelige effecten van schadelijke prikkels. Het lukt echter niet altijd om optimale bescherming aan te bieden zonder gebruik te maken van invasieve technieken, zoals epidurale anesthesie, of hogere doseringen van anesthesiemiddelen. Dit laatste kan leiden tot hemodynamische instabiliteit en verlengde nawerking. Daarom worden ook wel farmaca, die zelf geen anesthetische werking hebben, gebruikt als anesthetisch adjuvans. α_2-Adrenerge agonisten worden steeds meer genoemd als mogelijk anesthetisch adjuvans omdat zij kalmering veroorzaken, alsmede vermindering van angst, misselijkheid en pijn. (hoofdstuk 3). Deze effecten treden met name op bij recent ontwikkelde stoffen die een hogere selectiviteit hebben voor de α_2-receptoren dan de "klassieke" α_2-agonist clonidine.

De bovengenoemde effecten van dexmedetomidine en andere α_2-adrenerge agonisten worden veroorzaakt door stimulatie van α_2-adrenerge receptoren die zich bevinden in hersen centra zoals de locus coeruleus.

α_2-Receptoren bevinden zich echter ook in de vaatwand, waar ze vaatvernauwing veroorzaken. Sommige dierexperimentele studies suggereerden dat α_2-adrenerge stimulatie nadelige vasoconstrictie kan veroorzaken van perifere en coronaire bloedvaten. Daarom hebben wij, voordat wij dexmedetomidine wensten te gebruiken tijdens klinische anesthesie, eerst zijn hemodynamische effecten op het normale cardiovasculaire systeem onderzocht. Om meer gedetaillerde studies aangaande coronaire doorbloeding en zuurstofgebruik van het hart te kunnen verrichten hebben wij de effecten van dexmedetomidine op het cardiovasculaire systeem van honden en geiten onderzocht. Daarna hebben wij een klinische studie verricht met als doel cardiovasculaire effecten en de voordelen van dexmedetomidine te evalueren in gezonde patiënten die een kleine operatie moesten ondergaan.

In hoofdstuk 4 vergeleken wij de hemodynamische effecten van clonidine met dexmedetomidine in honden bij een aantal doseringen. Beide stoffen veroorzaakten een tijdelijke verhoging van de arteriële bloeddruk en de systemische vaatweerstand, een langer durende verlaging van het hartminuutvolume en de hartfrekwentie. Dexmedetomidine bleek 3 tot 10 keer potenter te zijn dan clonidine voor wat betreft de

pressor effecten. Binnen 15 min na toediening verminderde het pressor effect van dexmedetomidine en clonidine aanzienlijk bij doseringen ≤ 3 μg/kg. Hoge doses clonidine (10 en 30 μg/kg) veroorzaakten langdurige coronaire vasoconstrictie alsmede verminderde myocardiale contractiliteit. Deze resultaten geven aan dat langzame intraveneuze toediening belangrijker is bij de potente en selectieve α_2-adrenerge agonist dexmedetomidine dan bij clonidine, en dat dexmedetomidine de α_1-adrenerge effecten mist die na hoge dosis clonidine voorkomen.

In hoofdstukken 5 en 6 beschrijven wij de hemodynamische effecten van dexmedetomidine in honden onder chloralose/urethane of fentanyl/halothane anesthesie. De snelle, tijdelijk verhoogde bloeddruk, systemische vasculaire weerstand en linker kamer eind-diastolische druk, alsmede de langer durende vermindering in hartminuutvolume en hart- frekwentie waren vergelijkbaar in de twee groepen. Vijftien minuten daarna was het effect afhankelijk van de gebruikte anesthesietechniek. In de chloralose/urethane groep daalde de bloeddruk, terwijl in de fentanyl/halothane groep de bloeddruk hoog bleef. De vorm van anesthesie beinvloedt dus de cardiovasculaire effecten van dexmedetomidine in honden. Omdat bekend is dat de sympathische tonus hoger is onder chloralose/urethane anesthesie, is het waarschijnlijk dat de stabiliserende effecten van dexmedetomidine op hartfrekwentie en bloeddruk groter zijn in situaties met een hogere initiële sympathische tonus.

Dit stabilizerende effect van dexmedetomidine in de chloralose/urethane groep ging gepaard met verminderde energie behoefte van het myocard, terwijl de myocardiale zuurstof toevoer verminderde parallel aan de zuurstofbehoefte. Myocardiale zuurstofextractie ging alleen omhoog na de hoogste dosis van 10 μg/kg dexmedetomidine, maar zelfs na deze dosering extraheerde het hart lactaat, wijzend op de afwezigheid van globale myocardiale ischemie. Deze gegevens wijzen erop, dat voor dexmedetomidine ≤ 3 μg/kg de vermindering van myocardiale doorbloeding functioneel is, dat wil zeggen veroorzaakt is door verminderde metabole behoeften en niet door adrenerge vasoconstrictie. Bovendien was de afname van de myocardiale doorbloeding het sterkst in de buitenste lagen van de linker kamerwand en minder uitgesproken in de binnenste lagen, de lagen die het meest gevoelig zijn voor ischemie (hoofdstuk 5).

Ook het effect van dexmedetomidine op de doorbloeding van veel andere organen is onderzocht (hoofdstuk 6). Het bleek dat de reductie in hartminuutvolume door dexmedetomidine gepaard gaat met sterke verschillen in de veranderingen van doorbloeding van de verschillende organen. Doorbloeding van de vitale organen (hart, hersenen, nieren) wordt gespaard, terwijl de doorbloeding van minder vitale organen, zoals huid, ingewanden en milt, sterk afnemen, evenals de doorstroming van arterioveneuze anastomoses.

Nadat wij de cardiovasculaire effecten van dexmedetomidine bestudeerd hadden in honden, een species waarvan bekend is dat het erg gevoelig is voor α-adrenerge vasoconstrictie, onderzochten wij de geit. Het pressor effect van dexmedetomidine in

geiten bleek kortdurender dan in de hond, en daarmee meer vergelijkbaar was met dat in de mens. In geiten verminderde 10 μg/kg dexmedetomidine de myocardiale zuurstofextractie (hoofdstuk 7), terwijl in de hond deze dosis de extractie deed toenemen (hoofdstuk 5). Dit betekent dat de balans van zuurstofaanvoer en -behoefde in het myocard stabiel blijft, zelfs na een hogere dosis dexmedetomidine in geiten. Als de pressor respons (in de perifere circulatie) een maat is voor het effect in de coronair circulatie, is het mogelijk dat α_2 adrenerge coronaire vasoconstrictie in mensen minder uitgesproken is dan in honden.

Hierna is een klinische studie verricht bij gezonde volwassenen tijdens kleine chirurgische ingrepen. Dexmedetomidine werd toegediend in een dosering van 2 μg/kg intraveneus gedurende 5 min voor de inleiding van anesthesie. Deze dosis verminderde de benodigde hoeveelheid isofluraan met 90%, de benodigde hoeveelheid thiopental met 14% en die van fentanyl met 33%. Plasma catecholamine spiegels waren lager in patiënten met dexmedetomidine, wat wijst op verlaging van de sympatholytische activiteit. Dexmedetomidine verminderde de hemodynamisch reacties op intubatie en ontwaken uit de anesthesie, en verhoogde de hemodynamische stabiliteit in de perioperatieve periode. Verder was er een verminderde behoefte aan post-operatieve analgetica en anti-emetica. Ondanks het feit dat peri-operatieve bradycardie vaker voorkwam in de dexmedetomidine patiënten, heeft dit niet geleid tot ongewenste hemodynamische effecten (hoofdstuk 8).

Wij concluderen uit de bovenstaande gegevens dat de hemodynamische effecten van dexmedetomidine geen contraindicatie vormen voor zijn gebruik tijdens anesthesie. De centrale sympatholyse tesamen met de reductie van anesthetica, analgetica en anti-emetica geven aan dat dexmedetomidine een veel belovend middel is voor gebruik als anesthetisch adjuvans bij gezonde patienten.

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Curriculum Vitae

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Christopher John Lawrence was born on July 22nd, 1945 in Tunbridge Wells, England. He attended Chichester High School for Boys from 1956 to 1964, where he was School Captain from September 1963 till May 1964.

In 1964 he was awarded an Open Exhibition to study medicine at Christ Church Oxford, obtaining an honours degree in human physiology in June 1967. He continued his medical studies in Oxford and at University College Hospital Medical School in London. In January/February 1970 he visited University College Hospital, Ibadan, Nigeria on an exchange scholarship. He graduated in medicine at the University of Oxford in December, 1970, with the degrees of Batchelor of Medicine and Batchelor of Surgery (B.M., B.Ch., Oxon).

After appointments in surgery, internal medicine, obstetrics and Accident and Emergency, he commenced his training in anaesthesia at St. Richard's Hospital, Chichester in 1973, continuing in 1974 at the Shackelton Department of Anaesthesia at Southampton University Hospital (Professor John Norman), and becoming Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons of England in February, 1977.

In 1978 he joined the anaesthetic staff of the St. Annadal Hospital in Maastricht and since 1983 has been a staff member of the Department of Anaesthesia at the University Hospital of Maastricht.

List of Publications

Flacke JW, Lawrence CJ, Flacke WE, Prinzen FW, Scheinin M, de Lange S. Hemodynamic effects of dexmedetomidine in anesthetized dogs and their antagonism by ATP. *J Cardiothorac Anesth* 1990; **4** (6, Suppl 3): 97.

Flacke WE, Flacke JW, Lawrence CJ, Prinnzen FW, Floor E, de Lange S. Effects of dexmedetomidine and ATP on the coronary circulation and cardiac function in anesthetized dogs. *J Cardiothorac Anesthesia* 1990; **4** (6, Suppl 3): 47.

Lawrence CJ, Lestrade A, de Lange S. Isradipine, a calcium antagonist, in the control of hypertension following coronary artery-bypass surgery. *Am J Hypertension* 1991; **4** (2, Suppl 2): 207S–209S.

Prinzen FW, Lawrence CJ, de Lange S. Endo/epicardial blood flow ratio after infusion of specific alpha2-agonist dexmedetomidine in dogs. *Pfluegers Archive* 1991; **419**: R9.

Prinzen FW, van Leeuwen CJ, de Lange S. Effect of the specific α_2-adrenergic agonist dexmedetomidine on myocardial oxygen supply and demand in anesthetized dogs. *Pfluegers Arch* 1991; **420** (Suppl 1): R115.

Lawrence CJ, Prinzen FW, de Lange S. Effects of clonidine on the coronary circulation and cardiac function of anaesthetized dogs. *J Cardiothorac Vasc Anesth* 1992; **6** (1, Suppl 1): 75.

Lawrence CJ, Prinzen FW, de Lange S. Effects of the specific α_2-adrenergic agonist dexmedetomidine on the systemic and coronary circulation of the anaesthetized goat. *J Cardiothorac Vasc Anesth* 1992; **6** (1 Suppl 1): 76.

Lawrence CJ, Lestrade A, Chan E, de Lange S. Comparative study of isradipine and sodium nitroprusside in the control of hypertension in patients following coronary artery-bypass surgery. *Acta Anaesthesiol Scand* 1993; **37** (Suppl 99): 48–52.

Lawrence CJ, Prinzen FW, de Lange S. Comparison of the haemodynamic effects of the α_2-agonists clonidine and dexmedetomidine in the anaesthetized dog. *J Cardiothorac Vasc Anesth* 1994; **8** (3, Suppl 2): 32.

Lawrence CJ, Prinzen FW, van Leeuwen CJ, de Lange S. The haemodynamic effects of the α_2-agonist dexmedetomidine depend on the animal species and the anaesthetic agent used. *J Cardiothorac Vasc Anesth* 1994; **8** (3, Suppl 2): 83.

Prinzen FW, Lawrence CJ, van Leeuwen CJ, de Lange S. Effect of the α_2-adrenergic agonist dexmedetomidine on nutrient blood flow to various organs in anaesthetized dogs. *J Cardiothorac Vasc Anesth* 1994; **8** (3, Suppl 2): 82.

Prinzen FW, Lawrence CJ, van Leeuwen CJ, de Lange S. Effect of the α_2-adrenergic agonist dexmedetomidine on myocardial oxygen supply and demand in anaesthetized dogs. *J Cardiothorac Vasc Anesth* 1994; **8** (3, Suppl 2): 84.

Lawrence CJ, Prinzen FW, de Lange S. Effect of dexmedetomidine on the balance of myocardial energy requirement and oxygen supply and demand. *Anesth Analg* 1996; **82**: 544–50.

Lawrence CJ, Prinzen FW, de Lange S. The effect of the α_2-agonist dexmedetomidine on nutrient organ blood flow. *Anesth Analg* 1996; **83**: 1160–5.

Roekaerts PMHJ, Lawrence CJ, Prinzen FW, de Lange S. Alleviation of the peripheral hemodynamic effects of dexmedetomidine by the calium channel blocker isradipine. *Acta Anaesthesiol Scand* 1997; **41**: 364–70.

Lawrence CJ, Prinzen FW, de Lange S. Hemodynamic and coronary vascular effects of dexmedetomidine in the anesthetized goat. *Acta Anaesthesiol Scand* 1997; **41**: 830–6.

Lawrence CJ, de Lange S. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. *Anaesthesia* 1997; **52**: 736–44.